Exhibit E

1. CLINICAL STUDY REPORT OXN 2401

Study Title:	Optimization of Naloxone - Oxycodone Ratio in Pain Patients
Study Code	OXN2401
Indication Studied	Severe chronic pain of tumor and non-tumor origin
Study Design	Multicenter, prospective, controlled, randomized, double-blind (with placebo-dummy), 4 parallel group, phase 2 study
Test Drug:	Naloxone controlled release tablets 5 mg and 10 mg Oxycodone controlled release tablets 10 mg and 20 mg
Phase:	Phase 2
Sponsor:	Mundipharma GmbH Mundipharmastrasse 2 65549 Limburg (Lahn) Germany
Sponsor Contact:	Michael Hopp, Dr. med. Tel:+49 (0)64 31 701-438 E-mail: michael.hopp@mundipharma.de
Principal Investigator:	Wolfgang Fleischer, Dr. med. Mundipharmastrasse 2 65549 Limburg (Lahn) Germany Tel:+49 (0)64 31 701-400 wolfgang.fleischer@mundipharma.de
Start Date:	07-May-2002 (FPFV)
End Date:	12-Apr-2003 (LPLV)
Report Date:	03-Jun-2005
Report Status:	Final
GCP Statement:	This study was performed in full compliance with acceptable Good Clinical Practices (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.

2. SYNOPSIS

Name of Company: Mundipharma GmbH	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: n/a	Referring to Part IV of the Dossier	
Name of Active Ingredient: Oxycodone hydrochloride Naloxone hydrochloride	Volume: Page:	

Title of the Study: Optimization of Naloxone - Oxycodone ratio in pain patients

Investigator(s)/Center(s): This study was conducted by qualified investigators under the Sponsorship of Mundipharma GmbH at 28 sites in Germany. The principal investigator (LKP - Leiter der Klinischen Prüfung, principal investigator in Germany) was Dr. med. Wolfgang Fleischer. The signature of the principal investigator (LKP) is contained in Appendix 16.1.5.

Publication (Reference): None.

Study Dates:	**Study Status:**	**Phase of Development:**
07-May-2002 to 12-Apr-2003	Completed	Phase 2

Objectives: The primary objective of this study was to investigate whether an oxycodone/naloxone combination will lead to a comparable analgesia with a decrease in constipation in patients with severe chronic pain of tumor- and non-tumor origin when compared with oxycodone alone, and to investigate the optimal dose ratio of oxycodone and naloxone. The secondary objective was to compare the incidence of other side effects between treatment groups.

Methodology: This was a multicenter, prospective, controlled, randomized, double-blind (with placebo-dummy), 4 parallel group Phase 2 study with oral CR oxycodone, oral CR naloxone and corresponding naloxone placebo. The study had three core phases: a pre-randomization phase, a 4 week double-blind treatment period (maintenance phase) and a follow-up phase. The pre-randomization phase consisted of screening and titration/run-in. Following screening, patients entered either a titration or run-in period. Patients with insufficient pain control at screening entered a minimum 2 week titration period and were individually titrated and stabilized at an oxycodone dose between 40 and 80 mg per day. Patients on stable oxycodone pretreatment at screening (40-80 mg/day) and with concomitant constipation, entered a 1 week run-in period and were eligible for the maintenance phase without prior titration.. At the end of the titration/run-in period, patients who were receiving a stable maintenance dose of oxycodone (with no more than 5 rescue medication intakes per week) and had a medical need for the regular intake of laxatives were randomized to one of 3 naloxone treatment groups or a naloxone placebo treatment group and received their maintenance dose of oxycodone plus either 10 mg, 20 mg, 40 mg or naloxone placebo CR tablets daily. After the treatment period, patients maintained their maintenance dose of oxycodone only for a further two week follow-up phase.

Number of Patients: In total 202 patients were randomized and 152 patients were to receive both naloxone and oxycodone; 50 patients were to receive oxycodone and naloxone placebo. The ITT population consisted of 196 (97.0%) patients. The PP population consisted of 99 (49.0%) patients.

Indication and Criteria for Inclusion: Male or female patients, aged ≥18 years, who were suffering from severe chronic pain of tumor and non-tumor origin and who required opioid treatment were enrolled in the study. Patients with insufficient efficacy or tolerability to a WHO II or III analgesic and patients with stable oxycodone therapy (40-80 mg/day) were suitable for screening. Patients included in the double-blind treatment period were on stable oxycodone treatment and had a medical need for the regular intake of laxatives..

Statistical Methods: Summary statistics were provided for all outcome measures, either for the intent-to-treat (ITT) population or the per protocol (PP) population. The primary population for statistical analysis was the ITT population, with additional focus on the PP population for the analysis of pain intensity. For the primary efficacy outcomes, mean pain and bowel function, it was investigated if the addition of naloxone to oxycodone lead to an improvement in bowel function (test of difference) without a clinically relevant increase in pain intensity (confidence intervals and non-inferiority test). Hence, the influence of the absolute dose of naloxone (10 mg naloxone, 20 mg naloxone, 40 mg naloxone) on bowel function and pain intensity was tested in an exploratory way using t-tests with each dose compared with placebo. In order to take imbalances in mean pain intensity at baseline into account, the t-tests were based on an ANOVA analysis, and also on a post-hoc analysis on the ANCOVA, with the baseline value as covariate. In addition, response surface analysis was performed within an additional analysis for pain intensity and bowel function as well as for SOWS, global assessment of tolerability, and rescue medication intake. The response surface analyses, based on the before mentioned parameters, aimed to investigate the effect of the oxycodone/naloxone ratio. For the analysis of the secondary endpoints rescue medication, ease of defecation, feeling of incomplete bowel evacuation, judgment of constipation, laxative intake and sumscores of elicited opioid and naloxone typical side effects the Wilcoxon test (modified to handle the Behrens-Fischer problem) was used to test for treatment differences for the absolute dose of naloxone. In addition, for stool frequency and percentage change in mean laxative dose t-tests for the absolute dose of naloxone were performed for treatment differences. All calculated p-values were of an exploratory nature.

Results:

Efficacy: Overall, the treatment groups were generally balanced regarding demographic and baseline characteristics, anamnesis and medical profile. A total of 36 (17.8%) patients discontinued during the treatment or follow-up phase with the primary reason for discontinuation being an AE (19 patients, 9.4%). During the maintenance phase no apparent differences in the intensity of pain were observed between any treatment groups or dose ratios, indicating that there was no clinically meaningful influence of naloxone on the analgesic effect of oxycodone. By absolute naloxone dose (10mg, 20mg and 40 mg), mean pain score differences from naloxone placebo and 90% confidence intervals, in both the ITT and Per Protocol populations, did not indicate any clinically relevant differences in analgesic efficacy between oxycodone/naloxone and oxycodone alone. In the ITT population, mean pain scores (+-SD), ranged from 38.3 (±18.49) to 38.8 (±16.59) compared to 36.9 (±15.74) for placebo during the last 7 days prior to Visit 4 and 37.2 (±17.24) to 38.7 (±17.05) compared to 37.8 (±18.22) for placebo during the last 7 days at the end of the maintenance phase. Analgesic efficacy did not change at V4 and V5 with oxycodone dose or oxycodone/naloxone ratio in a quadratic response surface model using oxycodone dose and the ratio as factors and baseline mean pain as covariate. In a quadratic response surface model with oxycodone and naloxone dose as factors, it was demonstrated that there was no relevant effect of naloxone dose on analgesic efficacy at V4 and V5.

A trend towards improved mean bowel function with increased dose of naloxone was seen. During the last 7 days at the end of the maintenance phase, mean bowel function scores (±SD) were lowest (low score values represent low bowel dysfunction) with the 1/1 (21.9±22.25), 1.5/1 (21.8±21.35) and 2/1 (26.7±23.98) dose ratios (ITT population). Bowel function appeared to worsen as the amount of naloxone decreased (45.4 (±22.28), 40.3 (±23.09), 31.3 (±25.82) and 26.1 (±25.08) for placebo, 10 mg, 20 mg and 40 mg respectively at the end of maintenance – Visit 5) with statistically significant differences to placebo in favor of 20 mg and 40 mg naloxone at the end of maintenance ($p<0.05$, t-test for difference). The statistical significant improvement in the 20mg and 40mg doses vs naloxone placebo was also demonstrated when the Visit 4 value was carried forward for subjects with missing Visit 5 data. The 2/1 and the 1.5/1 ratios demonstrated significant differences compared to the corresponding oxycodone dose plus naloxone placebo at V4 and V5, based on statistical significance testing of the mean bowel function data modeled using the quadratic model. At Visit 5, the size of the improvement in bowel function estimated for each dose ratio, versus the corresponding oxycodone dose plus naloxone placebo, was 11.0 ($p = 0.0089$) for the 4/1 ratio, 13.4 ($p = 0.0042$) for 3/1, 16.2 ($p = 0.0005$) for 2/1 and 16.5 ($p = 0.0014$) for 1.5/1. The improvement estimated at 2/1 was superior by 5.2 units on the bowel function scale over 4/1 ($p = 0.0180$). The analysis of the estimated response model confirmed that bowel function at V4 and V5 remains relatively constant within the dose ratio.

The oxycodone/naloxone combination provided improvements in ease of defecation, feeling of incomplete bowel evacuation and judgment of constipation. The greatest improvements were seen at dose ratios of 1/1, 1.5/1 and 2/1 or an absolute dose of 40 mg. Improvements in ease of defecation were seen during the last 7 days at the end of the maintenance phase ($p<0.05$ for all doses of naloxone versus placebo) and during the last 7 days prior to Visit 4 ($p<0.05$ for 20 mg and 40 mg naloxone versus placebo) as the dose of naloxone increased. Improvements in feeling of incomplete bowel evacuation were seen during the last 7 days at the end of the maintenance phase ($p<0.05$ for 20 mg and 40 mg naloxone versus placebo) and during the last 7 days prior to Visit 4 ($p<0.05$ for 40 mg naloxone versus placebo) as the dose of naloxone

LIST OF TABLES IN SECTIONS 1 TO 13

Page

4. LIST OF ABBREVIATIONS

AE	Adverse event
ADR	Adverse drug reaction
AMG	"Arzneimittelgesetz", German Drug Law
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AP	Alkaline phosphatase
ATC	Anatomical therapeutic chemical
BtMG	"Betäubungsmittelgesetz", Drug Control Act
CI	Confidence interval
CPMP	Committee for Proprietary Medicinal Products
CR	Controlled release
CRF	Case report form
CRO	Contract research organization
CV	Curriculum Vitae
DCF	Data clarification form
ECG	Electrocardiogram
EG	"Europäische Gemeinschaft", European Community
ESR	Erythrocyte sedimentation rate
GCP	Good clinical practice
γ-GT	Gamma-glutamyltranspeptidase
GMP	Good manufacturing practice
GP	General practitioner
ICH	International Conference on Harmonization
IEC	Independent ethics committee
ITT	Intent-to-treat
LKP	Leiter der Klinischen Prüfung, principal investigator in Germany
LOCF	Last observation carried forward
MedDRA	Medical dictionary for regulatory affairs
NAS	Numerical analogue scale
NCR	No carbon required
NOS	Not otherwise specified
NSAID	Non steroidal anti-inflammatory drug
OOWS	Objective opioid withdrawal scale
PP	Per protocol
PRA	Pharmaceutical Research Associates GmbH
RBC	Red blood cell (count)
SAE	Serious adverse event
SAS	Statistical analysis system
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase (also AST)
SGPT	Serum glutamate pyruvate transaminase (also ALT)
SOPs	Standard operating procedures
SOWS	Subject opioid withdrawal scale
VAS	Visual analogue scale
WBC	White blood cell (count)
WHO/ WHO-DRL	World Health Organization/ WHO-drug reference list

No. 2 AMG and § 40 Section 4 AMG). Each patient was given a copy of the written information and an informed consent form. The patient was asked to sign the informed consent form at the screening visit (see Section 9.4) prior to any study-specific procedures being performed. The master versions of the patient written information and informed consent form are contained in Appendix 16.1.3.

6. INVESTIGATORS AND STUDY PERSONNEL

This study was conducted by qualified investigators under the Sponsorship of Mundipharma GmbH at 28 sites in Germany.

A list of all investigators, their study site numbers, and the number of patients at each site is contained in Appendix 16.1.4. The signature of the principal investigator (LKP) is contained in Appendix 16.1.5. The names of important site personnel and other participants in the study, along with curricula vitae are contained in Appendix 16.1.4.

Key personnel from the Sponsor involved in the clinical conduct of the study included Martina Frank, Dr. med. (Clinical Leader); Wolfgang Fleischer, Dr. med. (LKP); Thomas Zimmermann, Dr. med. (Head of Drug Safety); Bernhard Krain (Clinical Trials Manager); (Tanja Schmidt (Clinical Trials Manager from 24 June 2002 onwards); and Christian Ruckes (Principal Statistician). The CRO PRA was responsible for study monitoring, safety management, data management, statistical analysis and for the preparation of the clinical study report.

Audit certificates and audit information are contained in Appendix 16.1.8.

7. INTRODUCTION

Oxycodone is a semisynthetic narcotic analgesic (full opioid agonist) which has been available for clinical use since 1917 and is indicated in various severe pain syndromes (1-10). Similar to other narcotic agents, the mechanism of action is exerted via stimulation of opioid receptors (μ, κ and δ) of the descending inhibitory pain control system (11). Although oxycodone is effective in the management of pain, there is a risk of abuse by individuals who are dependent on opioids or who misuse opioids for non-therapeutic reasons (12). Therefore, the availability and use of oxycodone is restricted by the narcotic drug laws in Germany.

Previous experience with other opioids has demonstrated a decreased abuse potential when opioids are administered in combination with a narcotic antagonist, especially in patients who are ex-addicts (13,14). This therapeutic concept has been successfully applied in a combination product (Valoron N®) of the opioid tilidine and the opioid antagonist naloxone, a commercially available intravenous narcotic antagonist indicated for the blockade of exogenously administered opioids. This combined preparation is currently exempt from the restrictions imposed on narcotic drugs in Germany.

A clinical development program has been designed to provide evidence for an optimal dose ratio of oral, controlled release (CR) naloxone and oxycodone that still exerts sufficient analgesic activity with an improved safety profile (15). The co-administration of oxycodone with naloxone may offer specific advantages with regard to the known side effects of oxycodone (including a reduced frequency and intensity of constipation), a lower abuse potential compared with oxycodone administered alone and a reduction in the occurrence of tolerance to opioids. Several clinical investigations have shown that oral naloxone treatment leads to a significant improvement in opioid-associated constipation.

the dose of oxycodone could be adjusted during titration or run-in at regular intervals and investigators maintained compulsory telephone contact every 2nd day to assess pain control and make dose changes. At the end of the titration/run-in period, patients who were receiving a stable maintenance dose of oxycodone every 12 hours (with no more than 5 rescue medication intakes per week) and had a medical need for the regular intake of laxatives (to have at least 3 bowel evacuations/week) were randomized to one of 3 naloxone treatment groups or a naloxone placebo treatment group. They received their maintenance dose of oxycodone CR every 12 hours plus either 10 mg, 20 mg, 40 mg or naloxone placebo CR tablets every 12 hours. After the treatment period, patients maintained their maintenance dose of oxycodone only for a further two week follow-up phase.

Patients maintained a daily diary, and assessments of compliance, pain, constipation, stool frequency, stool consistency and laxation were made over the course of the study. In addition, routine safety laboratory investigations were performed and a global assessment of efficacy and tolerability was completed. The assessments or procedures carried out at all scheduled visits and telephone contacts, along with details on data recorded in the study diary, are provided in Section 9.4.

Study CRFs were used to record data from eligible patients (separate CRFs were provided for the pre-randomization phase and for the maintenance/follow-up phase). For ineligible patients (screening failures or patients who were not on stable oxycodone treatment at the end of the titration/run-in period) only the respective pre-randomization phase/screening CRFs were completed.

There were three amendments to the study protocol (Amendment 1: dated 8 February 2002; Amendment 2: dated 16 May 2002; Amendment 3 dated: 21 November 2002) (see Section 9.8.1, and Appendix 16.1.1). Major changes to study design were the documentation of symptoms and signs of opioid withdrawal (by the patient and investigator, respectively) and an additional assessment of safety laboratory parameters during the maintenance phase.

level (minimum 30% reduction from baseline visit (week 0) (18,19). For this purpose the numerical analogue scale (NAS) pain score was used as an assessment of pain intensity. The NAS is based on a patient rating of pain from 0 = no pain to 100 = worst imaginable pain, and was completed twice daily by each patient (in their diary) in the morning and evening 2 hours after study medication intake.

During the titration period the starting dose of oxycodone was dependent on previous pain medication. For patients who were receiving a WHO class II opioid as pretreatment titration was initiated with 10 mg CR oxycodone twice daily. Patients receiving a WHO class III opioid as pretreatment initiated titration with an oxycodone starting dose calculated using the following opioid conversion factors:

Conversion factors (oral dosing):

- Morphine: Oxycodone dose (mg/day) = Morphine dose x 0.5
- Buprenorphine: Oxycodone dose (mg/day) = Buprenorphine dose x 37.5
- Hydromorphone: Oxycodone dose (mg/day) = Hydromorphone dose x 4.0
- Fentanyl patch: A 25 µg/h Fentanyl patch was replaced by 10 mg CR oxycodone twice daily.

Starting doses administered were either 2 x 10 mg, 2 x 20 mg, 2 x 30 mg, 2 x 40 mg daily (every 12 hours). The starting dose could be adjusted every 2 days. The investigator made compulsory telephone calls to each patient every 2nd day during the titration period and during each telephone call an assessment of average pain during the last 2 days was recorded in the CRF (using the NAS), along with a record of any AEs (including opioid typical elicited AEs). The dose of oxycodone could be adjusted if considered necessary by the investigator (either 2 x 20 mg, 2 x 30 mg, 2 x 40 mg daily). If appropriate, an asymmetric dosing adjustment either in the morning or in the evening was possible.

For patients on stable oxycodone pretreatment between 40-80 mg/day at screening, no initial dose adjustments were performed at the baseline visit and the patient entered a 7-day run-in period. During the run-in period telephone contact was performed as described above, and dose adjustments were performed if considered necessary by the investigator.

All patients who entered the 2 week titration period or the 7-day run-in period were only eligible for the double-blind treatment period (maintenance phase) if they maintained a stable daily oxycodone dose of 40-80 mg for a concurrent 7 day period, had a medical need for the regular intake of laxatives to have at least 3 bowel evacuations/week and if they had no more than 5 rescue medication intakes per week (1 intake of rescue medication was defined as one 10 mg CR oxycodone tablet). Patients had to maintain a dose of oxycodone of either 2 x 20 mg daily or 2 x 30 mg daily or 2 x 40 mg daily for 7 days.

If after the minimum 2 week titration period or the 7-day run-in period the patient had not maintained stable pain control (dose adjustments were necessary), they were not eligible for the maintenance phase and had to be discontinued from the study.

Throughout the titration or the 7-day run-in period, laxatives could be taken as needed and patients were instructed that 3 stools per week should be passed at a minimum. Patients were also instructed not to drive a car while taking oxycodone.

on the safety profile of oxycodone was assessed with particular attention to the known adverse events of oxycodone and naloxone (see Section 9.4.4).

The efficacy measurement for pain intensity (NAS) is commonly used to evaluate pain, and its use conforms to the recommendations made by the Committee for Proprietary Medicinal Products (CPMP) in guidelines on clinical investigations of medicinal products for the treatment of nociceptive pain (Adopted: November 2002 (CPMP/EWP/612/00)) (20). The BFI was developed to assess constipation in the population of pain patients taking opioids based on literature data. A full validation program of the BFI is ongoing. In addition, other ratings of bowel function and global efficacy and tolerability have been chosen that are reliable measures of patient response and investigator assessment (see Section 9.4.2) (21-24). Discontinuation due to lack of efficacy or safety reasons, were included as a firm indication of inadequate patient response. Overall safety was closely monitored throughout the study.

Randomization was used in this trial to avoid bias in the assignment of patients to naloxone treatment, to increase the likelihood that known and unknown patient attributes (e.g. demographics and baseline characteristics) were evenly balanced across each naloxone treatment group and placebo treatment group and to enhance the validity of statistical comparisons across all treatment groups. Blinded naloxone treatment was used to reduce potential bias during data collection and evaluation of endpoints.

9.3. Selection of Study Population

It was planned to randomize a total of 180 patients (in- and outpatients) of either sex and any race, who were suffering from severe chronic pain of tumor and non-tumor origin and who required around the clock opioid treatment and who experienced constipation, for the study. Out of these 180 patients, 135 were to be randomized to a combination of CR oxycodone and CR naloxone and 45 to a combination of CR oxycodone and CR naloxone placebo. The study population was defined by the inclusion and exclusion criteria listed below.

9.3.1. Inclusion Criteria

Patients who were to be included in the study at screening were those:

- Aged ≥ 18 years
- With severe chronic pain of tumor and non-tumor origin that required opioid treatment
    - **and/or** insufficient efficacy with a WHO II or III analgesic
    - **and/or** insufficient tolerability with a WHO II or III analgesic
    - **or** patients under current stable oxycodone therapy (40-80 mg/day)
- Were capable of voluntary participation and of providing written informed consent (to participate in study and concerning "Datenschutz" (data protection) requirements)
- Could understand the requirements of the protocol and where willing and able to fulfill them.

Patients who were to be included in the maintenance treatment period (maintenance phase) after titration or run-in were those:

On stable oxycodone treatment 40-80 mg/day with no more than 5 rescue medication intakes (oxycodone) per week

TABLE 9.4.1. Schedule of Visits and Procedures

Phase	Pre-Randomization			Maintenance			Follow-up
Period	Screening	Titration/Run-in		Maintenance treatment			Oxycodone only
Study Visit	Screening (V1)	Baseline (V2)	Telephone contact[1]	End Titrat. (V3)	(V4)	End mainten. (V5)	End follow-up (V6)
At week	Week -1	Week 0		Visit 2 + 1-3 weeks	V3 + 1 week	V3 + 4 weeks	V5 + 2 weeks
Allowed deviation	Day -7 to -1	Day 0	Every 2nd day	± 5 days	V3 + 7 to 10 days	± 2 days	± 5 days
Written informed consent	X						
Inclusion/exclusion criteria	X	X		X2			
Demographics at screening	X						
Medical profile/review	X	X		X	X	X	
ECG	Not done						
Pregnancy test	X						
Physical examination	X	X		X	X	X	X
Safety laboratory		X		X5	X	X	
Anamnesis		X					
Pain NAS		X	X	X	X6	X6	
Documentation of constipation		X		X	X	X	X
Global efficacy and tolerability						X	
Patient identification handout		X					
Patient diary handout and/or check		X		X	X	X	X
Prior/concomitant medication	X	X		X	X	X	X
AE documentation			X	X	X	X	X
Pat. randomization				X			
Patient compliance check				X	X	X	X
Drug accountability				X	X	X	X
Dispense study medication		X3		X4	X4	X3	
Oxycodone dose adjustment			X				
Sending information letter to GP		X					

1: telephone contacts are mandatory every second day between baseline and end of titration and optional at other times. Oxycodone dose adjustment was not possible during the maintenance phase.
2: check eligibility for maintenance phase
3: open label oxycodone only
4: open label oxycodone plus double-blind naloxone
5: Additional safety laboratory assessment (optional)
6: Pain was recorded daily in patient diary only (no entries were made in the CRF)

- Physical examination
- Documentation of pain
- Documentation of constipation (bowel function)
- Blood/serum and urine samples for safety laboratory data**
- Explanation of mode of administration (twice daily intake of study medication, instructions/explanation of written patient instructions for drug intake)
- Documentation in patient notes that the patient was participating in a clinical study
- Family physician was informed that study patient had given informed consent and entered the study
- Appointment made for obligatory telephone contact (every 2nd day)
- Appointment made for next visit.

*The patient was provided with sufficient study medication for an average daily dose of 80 mg for the entire titration/run-in period.

**Safety laboratory evaluations - local laboratories were used for all laboratory evaluations (at Visits 2-5). Clinically significant pathologic values were recorded in the CRF. Hematology, chemistry, and urinalysis were performed (see Section 9.4.4.4 for details of evaluations performed).

Compulsory telephone contact

The investigator or study nurse contacted each patient every 2nd day during the titration/run-in period. The following evaluations or procedures were performed:

- Documentation of average pain intensity during the previous 2 days
- Dosage adjustment of oxycodone
- Documentation of AEs.

At all other times during the study telephone contact was optional.

9.4.1.2. Maintenance Phase

Details on the evaluations and procedures performed at all study visits during the maintenance phase are provided below.

9.4.1.2.1. Maintenance Treatment Period

Visit 3 - end of titration/run-in; start of maintenance phase

Visit 3 occurred 1-3 weeks after Visit 2 (± 5 days) and concluded with the randomization to double-blind CR naloxone treatment. For these patients:

- Handout of new diary to patient

- Physical examination
- Documentation of constipation (bowel function)
- Documentation of AEs
- Documentation of patient compliance concerning route and mode of administration
- Documentation of concomitant medication
- Blood/serum and urine samples for safety laboratory data
- Appointment made for next visit of maintenance phase.

Visit 5 - end of maintenance phase week 4

Visit 5 occurred 4 weeks after Visit 3 (± 2 days) and concluded the double-blind naloxone treatment. For these patients:

Dispensed

- New study medication (oxycodone only)
- Patient diaries (investigator collected previous diary).

Evaluations or procedures:

- Return and documentation of unused study medication
- Patient diary check (accuracy and completeness)
  - Return of patient diary
  - Handout of new diary to patient
- Physical examination
- Documentation of constipation (bowel function)
- Documentation of AEs
- Documentation of patient compliance concerning route and mode of administration
- Documentation of concomitant medication
- Documentation of global efficacy and tolerability assessment
- Blood/serum and urine samples for safety laboratory data
- Appointment for follow-up visit.

last 7 days in the patient diary. Bowel function was determined based on three distinct NAS recorded in the CRF at Visits 2-6:

- Ease of defecation during the last 7 days according to patient assessment (0 = easy/no difficulty, 100 = severe difficulty)
- Feeling of incomplete bowel evacuation during the last 7 days according to patient assessment (0 = not at all, 100 = very strong)
- Personnel judgment of patient regarding constipation during the last 7 days (0 = not at all, 100 = very strong).

Additional rating scales (see below) were utilized for the global assessment of tolerability/efficacy and preference, stool consistency, and signs (OOWS) and symptoms (SOWS) of withdrawal:

Global rating scale (completed at the end of the maintenance phase (Visit 5) and rated independently by the investigator and patient):

A. Global assessment of the efficacy of study medication:

1. Very Good
2. Good
3. Fairly Good
4. Moderate
5. Slightly Poor
6. Poor
7. Very Poor

B. Global assessment of the tolerability of study medication:

1. Very Good
2. Good
3. Fairly Good
4. Moderate
5. Slightly Poor
6. Poor
7. Very Poor

C. Preference for maintenance (oxycodone/naloxone combination) or titration/run-in (oxycodone only) regarding efficacy/tolerability of study medication:

1. Titration/run-in

- Feeling of incomplete bowel evacuation (NAS value from CRF)
- Judgment of constipation (NAS value from CRF)
- Stool frequency (recorded daily in patient diary)
- Stool consistency (recorded daily in patient diary)
- Laxative intake/mean laxative dose (calculated from CRF entries)
- Sumscores of elicited adverse events (calculated from CRF entries)
- Global assessment - efficacy/tolerability/preference (assessed at Visit 5).

9.4.3. Pharmacokinetic Assessments

Pharmacokinetic evaluations were not performed.

9.4.4. Safety Assessments

Safety assessments consisted of monitoring and recording all AEs and serious adverse events (SAEs), the performance of safety laboratory assessments (including a screening pregnancy test) and the performance of physical examinations.

9.4.4.1. Adverse Events

An AE was any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, including placebo, and which did not necessarily have a causal relationship with treatment.

Therefore, an AE could be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease
- Any deterioration in non-protocol-required measurements of laboratory value or other clinical test that resulted in symptoms, a change in treatment, or discontinuation from study drug.

All noxious and unintended responses to a medicinal product related to any dose were considered as adverse drug reactions (ADRs). An unexpected or newly occurring AE/ADRs were those that were not consistent with the applicable product information (data in the Investigator's Brochure or product information).

The phrase "response to a medicinal product" meant that a causal relationship between a medicinal product and an AE was at least a reasonable possibility, i.e. the relationship could not be ruled out.

Assessment of causality in suspected AEs was based on the following considerations: associative connections (time or place), pharmacological explanations, previous knowledge of the drug, presence of characteristic clinical or pathological phenomena, exclusion of other causes and/or absence of alternative explanations.

9.4.4.2. Serious Adverse Events

A SAE was any untoward medical occurrence that at any dose:

- Resulted in death;
- Was life-threatening;
- Required inpatient hospitalization or prolongation of existing hospitalization;
- Resulted in persistent or significant disability/incapacity; or
- Was a congenital anomaly/birth defect.

All SAEs had to be reported to the CRO PRA by facsimile within 24 hours of the event using a SAE report form. The SAE report form was filled out and signed by the investigator. In addition, the Sponsor was notified by PRA of SAEs, especially deaths, by e-mail. All clinically significant, newly occurring ADRs were reported to the Sponsor by the investigator within one business day using a completed SAE report form.

The Drug Safety Department of the Sponsor ensured that the leader of the clinical study (LKP), any appropriate Ethics committees and/or the responsible federal agency in Germany, were notified according to AMG.

Clinically significant pathologic findings or laboratory values that developed during application of the study medication and were ongoing at the final evaluation time point were followed-up until the event resolved (e.g. a normal laboratory value was obtained) or the event or sequelae stabilized. In the investigator site file forms for laboratory and other pathologic findings were available for the documentation of follow-up evaluations (see Appendix 16.1.2). Patients with SAEs had to be followed until the event resolved or the event or sequelae stabilized.

9.4.4.3. Other Significant Events

Other significant events were defined as AEs that were not serious but resulted in discontinuation, causally-related AEs (AEs with a definite, probable, possible or unknown/missing relationship to study drug) and AEs that were considered to be clinically notable by the investigator or Sponsor (e.g. pregnancies).

9.4.4.4. Laboratory Measurements

Clinical laboratory tests during the pre-randomization and maintenance phase were performed by local laboratories. In addition, all laboratory tests for the qualification of patients for entry into the study were also performed by local laboratories.

The Schedule of Visits and Procedures (Table 9.4.1) shows the time points at which safety laboratory assessments were performed (blood was collected for clinical laboratory tests and urine was collected for urinalysis).

Amendment 3 to Protocol OXN 2401, dated 21 November 2002, stipulated an additional assessment of safety laboratory parameters at Visit 4, approximately 1 week after the addition of naloxone therapy.

An additional assessment of safety laboratory parameters could be performed at Visit 3, at the end of the titration/run-in period. This assessment was optional and was not stipulated in the protocol. Additional Safety Laboratory Results pages were added to the CRF.

- Occurrence of intolerable AEs or ADRs
- The investigator becomes aware that a subject fulfills any of the exclusion criteria or no longer fulfills the inclusion criteria
- The subject persistently violates the protocol
- Technical reasons eg, the subjects moves.

9.5. Treatments

9.5.1. Treatments Administered

The treatments administered in the study were:

- 10 mg CR oxycodone tablets (open-label)
- 20 mg CR oxycodone tablets (open-label)
- 5 mg CR naloxone tablets (double-blind)
- 10 mg CR naloxone tablets (double-blind).

All medication that was used as test medication or comparator in this study was defined as study medication. The study medication was produced in accordance with Good Manufacturing Practice (GMP) guidelines. The medication was packed in blisters (CR oxycodone) and bottles (CR naloxone) and labeled according to German Drug law (§ 10 Section 10). For the pre-randomization phase oxycodone only was administered in starting doses of either 2 x 10 mg, 2 x 20 mg, 2 x 30 mg, 2 x 40 mg daily (tablets taken in the morning and evening), which could be adjusted every 2 days if pain control was inadequate (see Section 9.1). Only patients with stable pain control (40-80 mg oxycodone per day - 2 x 20 mg, 2 x 30 mg, 2 x 40 mg daily) during the end of the pre-randomization phase were randomized to one of 3 naloxone treatment groups or a naloxone placebo treatment group for a 4 week maintenance treatment period (maintenance phase):

Group 1: 2 x 20 mg or 2 x 30 mg or 2 x 40 mg oxycodone daily plus naloxone placebo (2 naloxone placebo tablets taken every morning and evening)

Group 2: 2 x 20 mg or 2 x 30 mg or 2 x 40 mg oxycodone plus 10 mg (one 5 mg naloxone tablet and one naloxone placebo tablet taken every morning and evening) naloxone per day

Group 3: 2 x 20 mg or 2 x 30 mg or 2 x 40 mg oxycodone plus 20 mg (one 10 mg naloxone tablet and one naloxone placebo tablet taken every morning and evening) naloxone per day

Group 4: 2 x 20 mg or 2 x 30 mg or 2 x 40 mg oxycodone plus 40 mg (two naloxone 10 mg tablets taken every morning and evening) naloxone per day.

For blinding purposes each patient received 2 tablets naloxone/placebo every morning and evening.

Patients maintained their previous dose of oxycodone (dose at the end of the pre-randomization phase) and the dose ratios in Table 9.5.1, below, were investigated.

TABLE 9.5.2. Study Drug Supplies

	Placebo	Oxycodone	Oxycodone	Naloxone	Naloxone
Dosage form	Tablet identical to naloxone 5 mg and 10 mg	CR Tablet	CR Tablet	CR Tablet	CR Tablet
Dose	Not applicable	10 mg	20 mg	5 mg	10 mg
Other ingredients	Kollidon 30, Lactose, Surerelease, Lanette 18, Mg-Stearat, Talkum	Oxycodone HCl	Oxycodone HCl	Naloxone HCl, Kollidon 30, Lactose, Surerelease, Lanette 18, Mg-Stearat, Talkum	Naloxone HCl, Kollidon 30, Lactose, Surerelease, Lanette 18, Mg-Stearat, Talkum
Manufacturer	Mundipharma GmbH	Napp Pharmaceuticals	Napp Pharmaceuticals	Mundipharma GmbH	Mundipharma GmbH
Batch/Lot number	OXN-086-01	10012443	10012302	OXN5-087-01	OXN10-088-01
Batch size	2 kg	Bulk	Bulk	2 kg	2 kg
Date of manufacture	04-Sept-2001	Aug-2001	July-2001	05-Sept-2001	06-Sept-2001
Expiration date	12-Dec-2003	12-Dec-2003	12-Dec-2003	12-Dec-2003	12-Dec-2003

investigator. Those were the reasons why there exist gaps in the random numbers in the study data base, as well as gaps in the randomization numbers within an investigator.

Three copies of the complete randomization list were drawn up. The randomization list allowed direct allocation of patient numbers to treatment. One copy of the randomization list was used for packaging, labeling, and assembling of the study medication and then locked. The second copy was given to the responsible controlled substances officer. The third copy was sealed by the study biostatistician. The randomization scheme and identification for each patient are presented in Appendix 16.2.

In the study protocol it was originally planned to replace drop-outs with patients having the same naloxone treatment assignment, in order to keep the number of completers balanced in each treatment group. It was planned that the replacement would be conducted by the sponsor's drug supplies department, such that no additional staff would be required to be unblinded. However, this procedure was omitted in order to minimize errors in providing double-blind study medication to the investigator.

9.5.5. Removal of Patients From Therapy or Assessment

Patients could withdraw consent to participate in the study at any time without giving a reason. Where a reason for withdrawal was given, this was documented in the CRF. The investigator could discontinue a patient from the study for one of the following reasons:

- Progression of ongoing disease or new disease that makes a continuation in the study impossible
- Application of prohibited concomitant medication (see Section 9.5.8)
- Occurrence of intolerable AEs or ADRs
- Existence of exclusion or lack of inclusion criteria becomes known
- Persistent protocol violations by patient
- Clinically significant elevations in liver function results (AP, SGOT, SGPT, γ-GT, total bilirubin)
- Clinically relevant signs of opioid withdrawal
- A clinically significant reduction of analgesic activity >30%, and patient requiring more than 5 doses of rescue medication within 3 days
- Technical reasons.

For patients who discontinued the study during the pre-randomization phase, prior to the administration of naloxone, the reason for discontinuation (e.g. insufficient therapeutic effect) was recorded in the CRF and any AEs were followed up as previously described (see Section 9.4.4). No other assessments were performed.

For patients who discontinued the study during the maintenance phase or follow-up phase the reason for discontinuation (e.g. insufficient therapeutic effect of study medication) was recorded in the CRF and any AEs were followed up. In addition, if 'signs of withdrawal' was recorded as the reason for discontinuation a separate 'Signs of Withdrawal' CRF page was completed by the investigator.

9.5.9. Treatment Compliance

Treatment compliance was assessed based on the dispensing and return of study medication tablets. Patients were instructed to return their unused medication at Visits 3-6 and the investigator kept an accurate running inventory of study drug (including details of receipt and dispensing). Study diaries were collected at Visits 3-6 and reviewed for completeness and accuracy.

For each patient a 'yes/no' response to the following compliance/drug accountability questions was recorded in the CRF at Visits 3-6:

- Patient diary completed?
- Remaining study medication including packaging returned?
- Specifications about intake of study medication in patient diary in agreement with taken/returned tablets/capsules (drug intake performed correctly)?
- Compliance concerning mode of administration (twice daily every 12 hours)?

A record of visit dates was also kept, along with deviations from visits, using Microsoft Excel tracking sheets. The tracking sheets are located in the Study Master File.

Treatment compliance during the study is discussed in Section 10.5 Extent of Exposure.

9.6. Data Quality Assurance

This study was organized, performed, and reported in compliance with either the Sponsors written procedures (protocol writing, CRF production, patient information and informed consent production, study medication labeling and shipment) or the Standard Operating Procedures (SOPs) of the CRO PRA (data management, monitoring, statistical analysis, study reporting), and in accordance with the requirements of national and international GCP guidelines.

The Sponsor contracted the CRO PRA to perform study monitoring, safety management, data management, statistical analysis and clinical study report writing. Monitoring included a review of investigator workbooks and verification of data in the CRF against source documents (source data verification was performed on all (100%) critical variables (patient number, initials, sex, primary outcome parameter, AEs) and for 20% of other variables for all recruited patients. The purpose of monitoring was to ensure protocol adherence, the accurate capture of clinical data, the accurate recording of drug accountability and to guarantee GCP at all centers.

All tables, figures and data listings included in this report were independently checked for consistency, integrity and accuracy by PRA and the Sponsor's Clinical Leader and Statistician .

9.6.1. Data Collection

Each center was supplied with CRFs and patient diaries, consisting of three-part no carbon required (NCR) paper. All data were continuously collected in the CRFs and patient diaries. The PRA monitor visited each investigational site on a regular basis to review the CRFs and patient diaries for completeness and accuracy, and to instruct site personnel to make any required corrections or additions. After all data had been checked by the monitor, the original top sheet and first NCR copy of the CRF and diary were forwarded to Document Management at PRA for data entry purposes. The bottom sheet was kept in the investigator's records. Each CRF was signed by the investigator to confirm that the data are correct and complete and that the study was conducted according to the protocol.

The following conventions regarding definitions, data handling, and analysis were defined:

All available data were considered in the descriptive and exploratory evaluations described in this section. Age, duration of pain-causing disease, duration of pain and duration of constipation were calculated relative to the date of the screening visit. For the calculation of duration of pain-causing disease, duration of pain and duration of constipation (independent from opioid intake and dependent on opioid intake) the following rule regarding incomplete dates was applied: If the day of a start date was missing this was set to 1. If the month of a start date was missing this was set to January of the corresponding year. In all other cases missing values were set to missing, an interpolation of missing values was not performed.

AEs with complete onset dates up to the date of randomization were assigned to the titration/run-in period; AEs with complete onset dates from one day after date of randomization up to the date of Visit 5 (end of the maintenance phase) were assigned to the maintenance phase; AEs with complete onset dates after date of Visit 5 (end of the maintenance phase) were assigned to the follow-up phase. Incomplete start and stop dates of AEs were not completed. AEs with incomplete start dates were assigned to the respective phase of the study according to the period categorizations recorded in the CRF (see Appendix 16.1.2).

An analysis of center effects was not performed and no approaches to deal with multiplicity were required or defined.

All calculated p-values were of an exploratory nature and all hypotheses tests were performed at a level of significance of $\alpha = 0.05$, for one sided non-inferiority tests and two sided tests of difference.

Where applicable, all continuous variables were summarized using the following descriptive statistics: n, mean, standard deviation, minimum, lower quartile, median, upper quartile, and maximum. The frequency and percentage of observed levels were reported for all categorical measures and, in general, all data were listed sorted by treatment (initially by ascending dose of oxycodone and then by ascending dose of naloxone), site, and patient and, when appropriate, by study day within patient. Data were also provided for patients without a stable dose of oxycodone prior to randomization.

In order to compare the dose response relationships between the various oxycodone and naloxone dose ratios, relevant results were grouped by the dose ratio of oxycodone and naloxone (40 mg/placebo, 60 mg/placebo, 80 mg/placebo, 1/1, 1.5/1, 2/1, 3/1, 4/1, 6/1, 8/1), the absolute dose of naloxone (placebo, 10 mg, 20 mg, 40 mg), and the absolute dose of naloxone given the same oxycodone/naloxone dose ratio (4/1, 10 mg naloxone and 20 mg naloxone, 2/1, 20 mg naloxone and 40 mg naloxone).

Certain data were also provided by the absolute dose of oxycodone (40 mg oxycodone, 60 mg oxycodone, 80 mg oxycodone, no stable dose of oxycodone).

During the maintenance phase, the patients were allowed to take rescue medication. This influenced the actual amount of oxycodone taken. Therefore, for the purposes of the statistical analyses, oxycodone dose groups were assigned as follows:

Assigned treatment

Patients were assigned to one of the scheduled dose groups (40 mg, 60 mg and 80 mg) according to the following rule: the mean daily oxycodone dose during the last 7 days prior to the end of maintenance visit (the sum of all oxycodone doses taken during the last 7 days prior to the end of maintenance visit divided by 7) was compared with the scheduled dose groups (40 mg, 60 mg and 80 mg). The respective patients were then assigned to the dose group closest to

- There were large deviations from the scheduled visits, i.e. the date of visit was outside the respective visit window. Only deviations from the visit windows of the maintenance phase visits (Visit 4 and 5) were regarded as major protocol violations. Deviations from the other visits were regarded as minor protocol violations. For the identification of major protocol violations, the visit windows for Visit 4 and 5 were slightly increased after a blinded review of the data [completed 06-June-2003] and were defined as follows:

  Visit 4 (during the maintenance phase): Visit 3 plus 6 to 12 days

  Visit 5 (at the end of the maintenance phase): Visit 3 plus 25 to 31 days

The following additional major protocol violations were identified after a blinded review of the data [completed 06-June-2003]:

- Patients who changed their scheduled dose of oxycodone during the maintenance phase or patients who entered the maintenance phase on unexpected doses of oxycodone.
- Patients with insufficient signs of constipation at randomization.
- Patients who received two different medication packages during the study (i.e. two different naloxone doses). Those patients were removed from the efficacy analysis and assigned within the safety analysis to their first received dose.
- Patients with a history of psychoses and were randomized.
- Patients who received forbidden medications (the use of opioid medication was regarded as a major protocol violation if it was taken at any time after the baseline visit. Opioid medication taken on the day of the baseline visit was forbidden medication, but was only regarded as a minor protocol violation).

All protocol violations and deviations from inclusion and exclusion criteria were listed for the screened population. Major protocol violations were summarized for the ITT population by the absolute dose of naloxone. The primary population for all analyses was the ITT population.

Discontinuations from the treatment and follow-up phase were listed and summarized in the safety population by reason and absolute dose of naloxone. In addition, discontinuations from the screening and titration/run-in period were also listed and summarized in the screened population by reason. In addition signs of withdrawal (as assessed by the investigator using the OOWS) and symptoms of withdrawal (as recorded by the patient in the patient diary using the SOWS) were listed for the safety population.

9.7.1.1.1. Demographic/Baseline Analyses

Summary statistics for demographics and baseline characteristics (age, sex, ethnic group, height, weight, body mass index, tumor patient (yes/no), anamnesis) were provided for the safety population grouped by dose ratio of oxycodone and naloxone, absolute dose of naloxone and absolute dose of naloxone given the same oxycodone/naloxone ratio using the information collected at the screening visit. Age was provided in years.

For baseline anamnesis the following parameters were analyzed: pain-causing disease, duration of pain-causing disease, duration of pain and duration of constipation (independent from opioid intake and dependent on opioid intake). Pain-causing disease was coded using MedDRA Version 5.0 and summarized by system organ class and preferred term. Duration of pain-causing disease, duration of pain and duration of constipation was given in months.

naloxone treatment). The model included baseline values (mean during the last 7 days prior to randomization for pain; mean assessing the last 7 days prior to randomization for bowel function) as a covariate, and oxycodone dose and naloxone dose as factors. The analysis was done twice: once with the stable oxycodone dose at the beginning of the maintenance phase (40 mg/day, 60 mg/day, 80 mg/day) and once with the oxycodone dose calculated as the mean of the total oxycodone doses per day (including rescue medication) during the last 7 days before the respective visit during or at the end of the maintenance phase. The analysis was performed via SAS PROC RSREG/PROC GLM and was displayed by SAS PROC G3D using the predicted response.

For the response surface analysis performed for mean pain during the last 7 days before the end of the maintenance phase visit and mean bowel function assessing the last 7 days before the end of maintenance phase baseline values (mean during the last 7 days prior to randomization for pain; mean assessing the last 7 days prior to randomization for bowel function) were used as a covariate.

The Wilcoxon test (modified to handle the Behrens-Fischer problem) was used for the analysis of some secondary endpoints (see below and Appendix 16.1.9 for further details). For the additional post-hoc analyses the above mentioned response surface methodology was used (see below for further details).

For patients in the ITT population who took more than 50 mg oxycodone per week as rescue medication or did not follow one of the scheduled oxycodone dosing regimens (excluded from the per protocol [PP] population), treatment categories (e.g. dose ratio of oxycodone and naloxone) were assigned individually after a blinded review of the data (see Appendix 16.1.9.2). Additionally, ANCOVA analyses with naloxone treatment as variable factor and baseline value as covariable were conducted post-hoc, as well as t-tests comparing naloxone placebo with each naloxone treatment group separately.

9.7.1.2.1. Primary Efficacy Variables

9.7.1.2.1.1. Mean Pain

Mean Pain was calculated for each study visit as the mean value of the patient's diary entries of the last 7 days. Summary statistics for mean pain during the last 7 days were provided for each study visit for the groupings dose ratio of oxycodone and naloxone, absolute dose of naloxone and absolute dose of naloxone given the same oxycodone/naloxone ratio. To test for non-inferiority, one-sided t-tests of the absolute dose of naloxone versus placebo with equivalence limit 8 on a NAS of 0-100 (defined as a clinically not relevant difference and chosen as the equivalence limit) were conducted for mean pain during the last 7 days before the end of the maintenance phase visit (after 4 weeks of naloxone treatment), i.e. the null hypothesis 'mean pain during the last 7 days in the test group - mean pain during the last 7 days in the control (placebo) group $\geq$ 8' was tested versus the alternative hypothesis 'mean pain during the last 7 days in the test group - mean pain during the last 7 days in the control (placebo) group < 8'. In addition, two-sided 90% confidence intervals (CI) for the difference in means between the treatment groups were provided. A response surface analysis was also performed for the end of the maintenance phase (after 4 weeks of naloxone treatment). These analyses were performed for the ITT and PP populations. Tests were also performed to explore mean pain at Visit 4 (after 1 week of naloxone treatment) for the ITT population.

To evaluate the effects of the titration/run-in period a paired t-test for difference was conducted for the mean pain intensity during the last 7 days before the end of titration/run-in, compared with the average pain intensity during the last 7 days before the baseline visit. This analysis was

were taken to display a surface plot of the whole dose range investigated. Moreover, a contour plot of the bowel function with a granulation of 10 was performed.

Within the additional post-hoc analysis, the mean bowel function was analyzed at Visit 4 and Visit 5 by a response surface analysis and displayed by response surface plots. The model-estimated responses were tabulated for daily oxycodone dose versus oxycodone / naloxone ratio, daily naloxone dose versus oxycodone / naloxone ratio, and daily oxycodone dose versus daily naloxone dose.

Mean bowel function was analyzed using the LOCF methodology for the ITT population. This was done for patients who completed Visit 4, but not Visit 5. For mean bowel function, this means that the bowel function value for Visit 4 was carried forward to Visit 5.

9.7.1.2.2. Secondary Efficacy Variables

All analyses were performed for the ITT population.

9.7.1.2.2.1. Daily Pain Intensity

Mean daily pain intensity was calculated from the morning and evening measurement recorded in the patient diary. Summary statistics for daily pain intensity were provided for each day of the maintenance phase for the ITT population for the groupings dose ratio of oxycodone and naloxone, absolute dose of naloxone and absolute dose of naloxone given the same oxycodone/naloxone ratio.

The mean values for daily pain intensity (mean ± 95% CI) during the maintenance phase were plotted against time by absolute dose of naloxone for the ITT population. Further graphs displayed the mean values for daily pain intensity (mean ± 95% CI) and the absolute dose of oxycodone dose (mean ± 95% CI) against time during the titration/run-in period for the titration phase population, and the mean values for daily pain intensity (mean ± 95% CI) during the follow-up phase against time by the absolute dose of oxycodone for the ITT population.

9.7.1.2.2.2. Rescue Medication

Mean dose of rescue medication was calculated for each study visit as the mean value of the rescue medication per day of the last 7 days (rescue medication was recorded in the patient diary). Summary statistics for mean rescue medication during the last 7 days were provided for each study visit for the groupings dose ratio of oxycodone and naloxone, absolute dose of naloxone and absolute dose of naloxone given the same oxycodone/naloxone ratio. In addition, Wilcoxon tests (modified to handle the Behrens-Fischer problem) of absolute dose of naloxone versus placebo were performed in the ITT population for mean values at Visit 4 (after 1 week of naloxone treatment) and for mean values at the end of maintenance phase (after 4 weeks of naloxone treatment).

Additional summary statistics were provided for the mean dose of rescue medication during the whole maintenance phase for the groupings dose ratio of oxycodone and naloxone, absolute dose of naloxone and absolute dose of naloxone given the same oxycodone/naloxone ratio.

Within the additional post-hoc analyses the mean dose of rescue medication at Visit 4, Visit 5, and during the whole maintenance phase was analyzed by a response surface analysis and displayed by response surface plots. The model-estimated response was tabulated for daily oxycodone dose versus oxycodone/ naloxone ratio, daily naloxone dose versus oxycodone/ naloxone ratio, and daily oxycodone dose versus daily naloxone dose.

naloxone, absolute dose of naloxone and absolute dose of naloxone given the same oxycodone/naloxone ratio.

For the additional post-hoc analyses the percentage of days with at least one diarrheal stool during the maintenance phase was displayed by oxycodone/naloxone ratio and by absolute naloxone dose.

9.7.1.2.2.8. Laxative Intake

Number of days with laxation during the last 7 days and the percentage of days with laxation during the last 7 days were calculated for each study visit. In addition, the percentage of days with laxation during the whole maintenance phase and during the follow-up phase was calculated. Entries from the medication record CRF page were used for all calculations (laxatives were identified by the WHO ATC code A06A). Summary statistics for the number of days with laxation during the last 7 days were provided for each study visit for the groupings dose ratio of oxycodone and naloxone, absolute dose of naloxone and absolute dose of naloxone given the same oxycodone/naloxone ratio. In addition, Wilcoxon tests (modified to handle the Behrens-Fischer problem) of absolute dose of naloxone versus placebo were performed in the ITT population for values at Visit 4 (after 1 week of naloxone treatment) and for values at the end of the maintenance phase (after 4 weeks of naloxone treatment).

Additional summary statistics were provided for the percentage of days with laxation during the whole maintenance phase for the groupings dose ratio of oxycodone and naloxone, absolute dose of naloxone and absolute dose of naloxone given the same oxycodone/naloxone ratio, and for the percentage of days with laxation during the follow-up phase by absolute dose of oxycodone. This analysis was performed using the ITT population.

9.7.1.2.2.9. Mean Laxative Dose

An analysis of the mean laxative dose during the last 7 days was performed for patients who took only one type of laxative during the entire study. Entries from the medication record CRF page were used for all calculations (laxatives were identified by the WHO ATC code A06A). Summary statistics for the percentage change in mean laxative dose during the last 7 days from the randomization visit to each study visit were provided for the groupings dose ratio of oxycodone and naloxone, absolute dose of naloxone and absolute dose of naloxone given the same oxycodone/naloxone ratio. A t-test for difference of absolute dose of naloxone versus placebo was performed for the percentage change in mean laxative dose during the last 7 days from the randomization visit to the end of the maintenance phase (after 4 weeks of naloxone treatment). In addition, two-sided 95% CIs for the difference in means between the treatments were provided. This analysis was performed using the ITT population.

9.7.1.2.2.10. Global Assessment - Efficacy and Tolerability, Preference

For the global assessment of efficacy, tolerability, and preference (assessed by the investigator and by the patient at the end of the maintenance phase) summary statistics for the groupings dose ratio of oxycodone and naloxone, absolute dose of naloxone and absolute dose of naloxone given the same oxycodone/naloxone ratio were provided for the ITT population.

Within the additional post-hoc analyses the investigator's and patient's assessment of tolerability were analyzed by a response surface analysis and displayed by response surface plots. Sample characteristics were presented by oxycodone / naloxone ratio and by absolute naloxone dose.

9.7.1.3.4. Clinical Laboratory Evaluations

Clinically significant pathologic laboratory values were recorded at baseline, randomization (optional), during the maintenance phase (Visit 4) and at the end of the maintenance phase.

Clinically significant pathologic laboratory values recorded in the CRF were listed and summarized by laboratory parameter and absolute dose of naloxone for the safety population.

9.7.1.3.5. SOWS

SOWS were recorded during the first seven days of the maintenance phase in the patient diary. For the additional post-hoc analyses the total score (=sumscore) of the SOWS items (for a more detailed description of the parameters see 9.4.2) was calculated for each patient and day. Additionally, for each patient the minimum, mean, and maximum of the seven daily total scores were calculated. These parameters were summarized via sample characteristics for each oxycodone/ naloxone ratio and absolute naloxone dose.

Assuming that a maximum of the seven daily scores of 14 (original assumption) or 23 (FDA assumption) indicating a significant withdrawal, the maximum scores were categorized. Absolute and relative frequencies of patients with maximum score greater than or equal to 14, and 23 respectively, were presented by oxycodone/ naloxone ratio and absolute naloxone dose.

The minimum, mean, and maximum scores were analyzed by a response surface analysis. The model-estimated responses were tabulated for daily oxycodone dose versus oxycodone/ naloxone ratio, daily naloxone dose versus oxycodone/ naloxone ratio, and daily oxycodone dose versus daily naloxone dose.

9.7.1.3.6. Sumscore of the Severity of Elicited Opioid Typical Adverse events

The sumscore of the severity of elicited opioid typical adverse events (nausea, emesis, sedation, skin reactions (pruritus, urticaria, other)) was calculated for each study visit as the sum of the scores assigned to each of the above mentioned AEs observed during the last 7 days. A score of 0 was assigned, if the respective side effect was not observed during the last 7 days, a score of 1 if the AE was mild, a score of 2 if the AE was moderate and a score of 3 if the AE was severe. If for one side effect more than one AE with different severities were recorded during the last 7 days, the worst severity was used (range: 0: no adverse events to 12: all 4 adverse events are severe). The respective adverse events were identified by the following MedDRA preferred terms: nausea (nausea, nausea aggravated), emesis (vomiting NOS, vomiting aggravated), sedation (sedation, sedation aggravated, somnolence, fatigue), and skin reactions (dermatitis allergic, dermatitis exfoliative NOS, eczema, mucocutaneous rash, rash generalized, rash NOS, photosensitivity reaction NOS, urticaria acute, sweating increased).

Summary statistics for the sumscore of the severity of elicited opioid typical adverse events during the last 7 days were provided for each study visit for the groupings dose ratio of oxycodone and naloxone, absolute dose of naloxone and absolute dose of naloxone given the same oxycodone/naloxone ratio. In addition, Wilcoxon tests (modified to handle the Behrens-Fischer problem) of absolute dose of naloxone versus placebo were performed in the ITT population for values at Visit 4 (after 1 week of naloxone treatment) and for values at the end of the maintenance phase (after 4 weeks of naloxone treatment).

Additional summary statistics were provided for the sumscore of the severity of elicited opioid typical adverse events during the whole maintenance phase for the groupings dose ratio of oxycodone and naloxone, absolute dose of naloxone and absolute dose of naloxone given the same oxycodone/naloxone ratio, and for the sumscore of the severity of elicited opioid typical

post-hoc analysis using response surface analysis was performed for the primary efficacy endpoints.

9.8.1. Protocol Amendments

Three amendments were made to protocol OXN 2401 (Appendix 16.1.1 'Protocol and Protocol Amendments'). This report incorporates all changes described in these amendments.

Amendment 1 (dated 8 February 2002) made the following changes:

- Symptoms of withdrawal were to be documented during the first 7 days of the maintenance phase (maintenance treatment period). These were recorded in the study diaries by each patient using the SOWS
- If the reason for study termination during the maintenance and follow-up phase was 'signs of withdrawal', the investigator was to assess which signs of withdrawal were present and record them in the CRF
- The minimum reduction in pain level (recorded using the NAS) during the 2-week titration period was increased from 20% to 30%. This increase was based on definitions of clinically meaningful improvements in pain (18,19)
- Two additional withdrawal criteria were included: clinically relevant signs of withdrawal and clinically significant reduction of analgesic activity > 30%, with patient requiring more than 5 doses of rescue medication within 3 days
- Patients were to be advised to limit their laxative intake to prevent diarrhea. However, laxative intake was to be restarted if bowel evacuation had not occurred within 3 days of the start of the maintenance phase (double-blind treatment period).

This amendment was instituted before the date of study start [07-May-2002].

Amendment 2 (dated 16 May 2002) made the following changes:

- The defined study design was altered to reflect the use of a 'placebo-dummy' for naloxone during the double-blind maintenance phase
- The inclusion criteria were altered so that patients with insufficient pain control with a WHO II or III analgesic were to be included
- The study-specific inclusion criteria (after end of titration/run-in) were altered so that eligible patients were required to have a medical need for regular laxative intake (to have at least 3 bowel evacuations per week)
- The exclusion criteria for prohibited concomitant diseases were clarified to include lung cancer and metastases, liver or renal carcinomas or metastases
- Additional laxatives were allowed during the course of the study. Laxative intake was recorded in the patient diaries and on the Medication Record page of the CRF
- The NAS scale replaced the visual analogue scale (VAS) for all judgments of pain intensity, constipation, and for pain intensity parameters recorded in the patient diaries. A scale of 0-100 was used for all parameters

For the analysis of major protocol deviations (see also Section 9.7.1.1) the visit windows for Visit 4 and 5 were slightly increased and were defined as follows:

Visit 4 (during the maintenance phase):	Visit 3 plus 6 to 12 days
Visit 5 (at the end of the maintenance phase):	Visit 3 plus 25 to 31 days

Due the small number of tumor patients (N=5), analyses in the subgroups tumor and non-tumor patients for the outcomes mean pain, daily pain intensity, judgment of constipation, laxative intake and mean laxative dose were omitted.

Of the140 patients in the ITT population who received only one laxative during the course of the study, approximately half were given with comparable units and dose frequencies. Laxative analysis was not omitted.

One patient (01 141) had one entry for stool consistency recorded as 'solid/diarrheal'. This assessment was made during follow-up and did not contribute to the endpoint 'Median stool consistency during the maintenance phase', therefore no assignment to either 'hard' or 'diarrheal' was made for the analysis. The recorded value appeared in the listings only.

Additional figures were requested showing an overlay of mean bowel function and mean pain during the maintenance phase. Figures were provided for the ITT and the PP population. The values obtained during the last 7 days before the end of the maintenance phase (mean ± 95% CI) were plotted against the oxycodone/naloxone dose ratio and the absolute dose of naloxone.

For the investigation of whether the bowel function depends on the oxycodone/naloxone ratio or the absolute naloxone dose, further figures (surface plot, contour plot) were printed for the whole dose range of the total dose oxycodone taken versus the given naloxone dose.

Although the protocol lists the following parameters as efficacy parameters, when writing the clinical study report, it was decided that it would be more appropriate to consider these parameters as safety parameters:

- Sumscore of severity of elicited opioid typical effects
- Sumscore of severity of elicited naloxone typical effects
- OOWS and SOWS.

OOWS data were available for 4 patients only. Therefore, no analysis of OOWS was performed.

After the data were unblinded, additional post-hoc analyses were planned and performed. A detailed description of the additional post-hoc analyses performed is provided in the respective sections of Section 9.7.

This report incorporates all changes described in this section.

9.8.3. Database Errata

Not applicable.

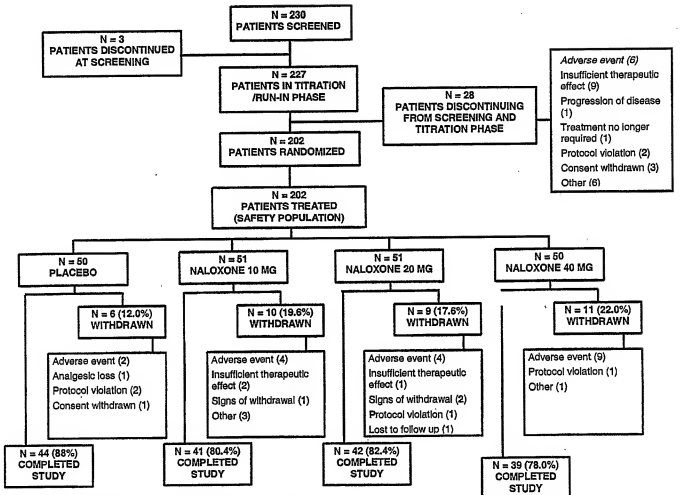

FIGURE 10.1. Patient Disposition by Absolute Dose of Naloxone

Cross-reference: Section 14.1, Tables 10.1-1, 10.1-2 and 10.3-1

10.2. Protocol Deviations

Major protocol deviations are presented in Table 10.2-1, Section 14.1. All protocol deviations are in Listings 10.2-1 and 10.2-2, Appendix 16.2.

Major protocol deviations were defined prior to unblinding the database. Patients reporting major protocol deviations were not included in the PP population. A full list of protocol deviations is in Section 9.7.1.1.

All reasons for exclusion from the PP population grouped by the absolute dose of naloxone are provided in Table 10.2. It was possible for more than one protocol deviation to be reported for one patient.

There were a total of 125 major protocol deviations.,

10.3. Data Sets Analyzed

Table 10.3 below summarizes the number and percentage of patients grouped by the absolute dose of naloxone for each analysis population. The populations for analysis are summarized in Table 10.3-1, Section 14.1 and full details of all patients in each analysis population are provided in Listing 10.3-1, Appendix 16.2. The randomization schedule is provided in Listing 10.3-2, Appendix 16.2. The populations included in the efficacy and safety analyses are defined in Section 9.7.1.1.

All randomized patients (N=202) received study medication and were included in the safety population. An ITT analysis was performed for all efficacy endpoints. The ITT population consisted of 196 (97.0%) patients. Six patients were excluded from the ITT population but included in the safety population for analysis of safety endpoints. Five patients (01 162, 09 053, 09 104, 14 069 and 25 214) were excluded due to missing post-baseline efficacy assessments and one patient (27 252) received two different medication packages and therefore two different naloxone doses during the course of the study. The PP population consisted of 99 (49.0%) patients.

TABLE 10.3. Number and Percentage of Patients in Analysis Populations

	Absolute Dose of Naloxone				
Population	Naloxone Placebo	Naloxone 10 mg	Naloxone 20 mg	Naloxone 40 mg	Total
Screened					230
Titration					227
Randomized	50 (100%)	51 (100%)	51 (100%)	50 (100%)	202 (100%)
Safety	50 (100%)	51 (100%)	51 (100%)	50 (100%)	202 (100%)
ITT	50 (100%)	49 (96.1%)	49 (96.1%)	48 (96.1%)	196 (97.0%)
Per protocol	29 (58.0%)	26 (51.0%)	22 (43.1%)	22 (44.0%)	99 (49.0%)

Cross-reference: Section 14.1, Table 10.3-1

Patients were randomized in balanced blocks to 3 naloxone treatment groups (10 mg, 20 mg and 40 mg) or a naloxone placebo group. Therefore, patients received their maintenance dose of oxycodone plus naloxone and were not randomized to dose ratio groups. As a result the dose ratio groups are imbalanced with regard to the number of patients within each ratio. Patient numbers in the safety population by dose ratio were 17, 17, 16, 15, 18, 34, 18, 33, 12 and 22 for 40 mg/placebo, 60 mg/placebo, 80 mg/placebo, 1/1, 1.5/1, 2/1, 3/1, 4/1, 6/1 and 8/1 respectively. For the ITT population patient numbers were 17, 17, 16, 15, 17, 32, 17, 32, 11 and 22 for 40 mg/placebo, 60 mg/placebo, 80 mg/placebo, 1/1, 1.5/1, 2/1, 3/1, 4/1, 6/1 and 8/1 respectively.

10.4. Demographics and Baseline Characteristics

Patient demographics and baseline characteristics are summarized in Table 10.4A below, and in Tables 10.4-1.1, 10.4-1.2 and 10.4-1.3, Section 14.1, by oxycodone/naloxone dose ratio, absolute dose of naloxone and by absolute dose of naloxone given the same oxycodone/naloxone dose ratio and in Listing 10.4-1 in Appendix 16.2. Baseline anamnesis (pain causing disease) is summarized by oxycodone/naloxone dose ratio, absolute dose of naloxone and by absolute dose of naloxone given the same oxycodone/naloxone dose ratio in Tables 10.4-2.1, 10.4-2.2 and 10.4-2.3, Section 14.1. Duration of anamnesis by oxycodone/naloxone dose ratio, absolute dose of naloxone and by absolute dose of naloxone

TABLE 10.4A. Patient Demographics and Other Baseline Characteristics by Absolute Dose of Naloxone - Safety Population

	Absolute Dose of Naloxone				
	Naloxone Placebo	Naloxone 10 mg	Naloxone 20 mg	Naloxone 40 mg	Total
Characteristic	N=50 (100%)	N=51 (100%)	N=51 (100%)	N=50 (100%)	N=202 (100%)
Sex n (%)					
Male	19 (38.0)	18 (35.3)	17 (33.3)	21 (42.0)	75 (37.1)
Female	31 (62.0)	33 (64.7)	34 (66.7)	29 (58.0)	127 (62.9)
Age [years]					
Mean	53.8	58.4	56.0	57.0	56.3
SD	12.74	12.75	12.65	14.03	13.06
Median	53.0	57.0	56.0	57.5	55.0
Min-Max	29 - 84	28 - 86	33 - 80	27 - 78	27 - 86
Race n (%)					
Caucasian	50 (100.0)	51 (100.0)	51 (100.0)	50 (100.0)	202 (100.0)
Black	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weight (kg)					
Mean	75.88	77.65	81.76	80.14	78.87
SD	13.43	14.47	13.92	18.11	15.14
Median	75.0	80.0	81.0	81.0	80.0
Min-Max	46 - 107	47 - 105	56 - 115	45 - 110	45 – 115
Height (cm)					
Mean	168.7	169.6	169.4	169.0	169.2
SD	8.29	8.00	7.97	9.12	8.30
Median	168.0	168.0	170.0	168.5	169.0
Min-Max	155 - 190	154 - 191	155 - 185	147 - 189	147 - 191
BMI (kg/m^2)					
Mean	26.70	27.03	28.65	27.93	27.58
SD	4.58	5.11	5.50	5.57	5.22
Median	26.03	25.83	27.78	28.09	26.61
Min-Max	17.1 – 40.3	17.3 – 37.2	18.9 – 42.6	16.8 – 39.8	16.8 – 42.6
Tumor patient n (%)					
Yes	1 (2.0)	1 (2.0)	1 (2.0)	2 (4.0)	5 (2.5)
No	49 (98.0)	50 (98.0)	50 (98.0)	48 (96.0)	197 (97.5)

Cross-reference: Section 14.1, Table 10.4-1.2

Table 10.4B presents a summary of baseline anamnesis grouped by the dose ratio of oxycodone and naloxone. Overall, back pain was the most common pain-causing disease (49 out of 202, 24.3%), followed by postoperative complications.

For all dose ratio groups the mean values for duration of pain causing disease and the duration of pain varied considerably between individual patients, mean values for each dose ratio ranged from 94.9 months to 122.3 months and 103.5 months to 174.7 months for each parameter respectively (Table 10.4B). The duration of pain causing disease for the absolute dose of naloxone groups ranged from 97.1 months to 118.5 months and the duration of pain ranged from 113.1 months to 154.7 months (Table 10.4-3.2, Section 14.1). The mean duration of constipation independent of opioid intake also varied between dose ratios and treatment groups, but was markedly lower in the 40 mg/placebo group (Table 10.4B) and the naloxone placebo group (Table 10.4-3.2, Section 14.1). The mean duration of constipation dependent on opioid intake was lowest in the 1/1 dose ratio group (Table 10.4B) and the 10 mg naloxone group (Table 10.4-3.2, Section 14.1).

Table 10.4C presents a summary of concomitant illness and previous disease reported for ≥ 10% of patients in any dose ratio group, grouped by the dose ratio of oxycodone and naloxone. There were no relevant differences in concomitant illnesses and previous diseases between the treatment groups. Hypertension NOS was the most common concomitant disease reported for 66 out of 202 (32.7%) patients. A range of 13 (26.0%) to 20 (39.2%) patients in each treatment group reported hypertension NOS (Table 10.4-4.2, Section 14.1). Apart from depression (45 patients, 22.3%) all other concomitant diseases were reported in less than 15% (30 patients) of all patients (Table 10.4C).

TABLE 10.4D. Anamnesis by Oxycodone/Naloxone Dose Ratio - Safety Population

Characteristic	Dose Ratios									
	40 mg/ Placebo	60 mg/ Placebo	80 mg/ Placebo	1/1	1.5/1	2/1	3/1	4/1	6/1	8/1
	N=17 (100%)	N=17 (100%)	N=16 (100%)	N=15 (100%)	N=18 (100%)	N=34 (100%)	N=18 (100%)	N=33 (100%)	N=12 (100%)	N=22 (100%)
Pain-causing disease* n (%)										
Back Pain	4 (23.5)	3 (17.6)	4 (25.0)	3 (20.0)	1 (5.6)	8 (23.5)	5 (27.8)	11 (33.3)	5 (41.7)	5 (22.7)
Postoperative complications NOS	5 (29.4)	1 (5.9)	5 (31.3)	2 (13.3)	4 (22.2)	6 (17.6)	0 (0.0)	4 (12.1)	1 (8.3)	3 (13.6)
Inverterbral disc herniation	5 (29.4)	0 (0.0)	1 (6.3)	0 (0.0)	2 (11.1)	2 (5.9)	0 (0.0)	2 (6.1)	0 (0.0)	2 (9.1)
Duration of pain-causing disease [months]										
N	17	16	16	14	18	33	18	33	12	22
Mean	94.9	112.8	117.6	99.2	103.8	110.5	122.3	99.7	107.0	99.8
SD	73.93	138.1	118.1	106.5	114.0	111.8	154.6	89.79	121.4	100.2
Median	80.0	75.5	78.0	64.0	56.0	60.0	60.0	72.0	55.5	83.0
Min-Max	11-264	0-594	2-459	5-325	17-469	11-424	17-687	11-361	1-376	2-393
Duration of pain [months]										
N	17	16	15	13	18	33	18	33	11	20
Mean	124.7	174.7	149.9	103.5	171.0	147.2	122.9	145.4	108.7	111.8
SD	105.1	172.2	123.8	87.31	176.1	117.4	86.86	139.5	93.72	94.35
Median	80.0	128.5	130.0	101.0	73.5	96.0	99.5	94.0	90.0	89.5
Min-Max	12-335	12-594	2-459	6-325	28-637	11-424	28-372	12-677	6-336	2-393
Duration of constipation (indep. from opioid intake) [months]										
N	4	4	3	1	4	11	5	7	4	7
Mean	35.5	127.0	127.3	209.0	274.5	143.1	168.2	119.4	130.3	196.1
SD	71.00	86.29	177.5	-	265.5	173.0	215.4	181.4	217.7	260.2
Median	0.0	124.0	34.0	209.0	281.5	46.0	49.0	20.0	32.0	90.0
Min-Max	0-142	46-214	16-332	209-209	19-516	9-491	0-512	1-485	1-456	3-729
Duration of constipation (dep. on opioid intake) [months]										
N	15	15	15	13	16	28	14	32	10	20
Mean	11.5	18.0	20.5	7	15.1	17.9	24.6	11.2	19.0	14.1
SD	15.89	21.85	32.25	8.69	16.20	24.38	22.38	16.13	16.07	18.99
Median	4.0	10.0	6.0	5.0	11.0	10.0	16.5	4.5	16.0	4.0
Min-Max	0-55	0-68	0-114	0-27	0-47	0-117	0-69	0-77	0-51	0-61

Cross-reference: Section 14.1, Tables 10.4-2.1 and 10.4-3.1

*Diseases reported for ≥20% of patients in any dose ratio group

TABLE 10.4F. Concomitant Illnesses and Previous Diseases by Oxycodone/Naloxone Dose Ratio (only diseases reported for ≥10% of patients in any dose ratio group) and Preferred Term - Safety Population

	Dose Ratios									
Preferred term	40 mg/ Placebo N=17 (100%)	60 mg/ Placebo N=17 (100%)	80 mg/ Placebo N=16 (100%)	1/1 N=15 (100%)	1.5/1 N=18 (100%)	2/1 N=34 (100%)	3/1 N=18 (100%)	4/1 N=33 (100%)	6/1 N=12 (100%)	8/1 N=22 (100%)
Hypertension NOS	5 (29.4)	5 (29.4)	3 (18.8)	6 (40.0)	5 (27.8)	10 (29.4)	8 (44.4)	12 (36.4)	4 (33.3)	8 (36.4)
Depression	3 (17.6)	4 (23.5)	4 (25.0)	2 (13.3)	7 (38.9)	6 (17.6)	5 (27.8)	8 (24.2)	1 (8.3)	5 (22.7)
Sweating increased	1 (5.9)	1 (5.9)	4 (25.0)	2 (13.3)	2 (11.1)	7 (20.6)	2 (11.1)	4 (12.1)	2 (16.7)	3 (13.6)
Sedation	2 (11.8)	1 (5.9)	5 (31.3)	1 (6.7)	0 (0.0)	4 (11.8)	2 (11.1)	7 (21.2)	1 (8.3)	3 (13.6)
Nausea	3 (17.6)	1 (5.9)	2 (12.5)	1 (6.7)	3 (16.7)	3 (8.8)	3 (16.7)	4 (12.1)	1 (8.3)	3 (13.6)
Back pain	1 (5.9)	2 (11.8)	3 (18.8)	0 (0.0)	2 (11.1)	3 (8.8)	0 (0.0)	3 (9.1)	2 (16.7)	1 (4.5)
Diabetes mellitus	1 (5.9)	1 (5.9)	2 (12.5)	1 (6.7)	2 (11.1)	4 (11.8)	1 (5.6)	2 (6.1)	0 (0.0)	1 (4.5)
Hypercholesterolaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	6 (33.3)	2 (5.9)	1 (5.6)	3 (9.1)	0 (0.0)	2 (9.1)
Obesity	2 (11.8)	1 (5.9)	1 (6.3)	3 (20.0)	3 (16.7)	3 (8.8)	0 (0.0)	1 (3.0)	0 (0.0)	1 (4.5)
Vertigo	2 (11.8)	0 (0.0)	2 (12.5)	0 (0.0)	2 (11.1)	2 (5.9)	1 (5.6)	4 (12.1)	0 (0.0)	2 (9.1)
Headache NOS	3 (17.6)	0 (0.0)	2 (12.5)	1 (6.7)	0 (0.0)	1 (2.9)	0 (0.0)	1 (3.0)	2 (16.7)	3 (13.6)
Migraine NOS	3 (17.6)	1 (5.9)	0 (0.0)	1 (6.7)	0 (0.0)	1 (2.9)	2 (11.1)	2 (6.1)	1 (8.3)	2 (9.1)
Insomnia	1 (5.9)	1 (5.9)	2 (12.5)	0 (0.0)	1 (5.6)	3 (8.8)	0 (0.0)	2 (6.1)	0 (0.0)	2 (9.1)
Restlessness	1 (5.9)	0 (0.0)	2 (12.5)	0 (0.0)	1 (5.6)	3 (8.8)	2 (11.1)	1 (3.0)	1 (8.3)	1 (4.5)
Muscle cramps	2 (11.8)	1 (5.9)	1 (6.3)	0 (0.0)	1 (5.6)	0 (0.0)	2 (11.1)	1 (3.0)	1 (8.3)	2 (9.1)
Acquired hypothyroidism	1 (5.9)	2 (11.8)	1 (6.3)	2 (13.3)	1 (5.6)	2 (5.9)	0 (0.0)	1 (3.0)	0 (0.0)	1 (4.5)
Gastritis NOS	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	1 (5.6)	4 (12.1)	0 (0.0)	2 (9.1)
Fibromyalgia	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	2 (11.1)	3 (8.8)	0 (0.0)	2 (6.1)	1 (8.3)	0 (0.0)
Hyperuricaemia	1 (5.9)	1 (5.9)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	4 (12.1)	0 (0.0)	2 (9.1)
Vomiting NOS	1 (5.9)	2 (11.8)	0 (0.0)	1 (6.7)	0 (0.0)	2 (5.9)	1 (5.6)	0 (0.0)	0 (0.0)	2 (9.1)
Osteoporosis NOS	0 (0.0)	0 (0.0)	1 (6.3)	2 (13.3)	2 (11.1)	0 (0.0)	1 (5.6)	2 (6.1)	0 (0.0)	0 (0.0)
Goitre	1 (5.9)	1 (5.9)	0 (0.0)	1 (6.7)	2 (11.1)	3 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain NOS	1 (5.9)	0 (0.0)	2 (12.5)	0 (0.0)	1 (5.6)	0 (0.0)	1 (5.6)	1 (3.0)	0 (0.0)	1 (4.5)
Localised osteoarthritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	2 (5.9)	1 (5.6)	1 (3.0)	2 (16.7)	0 (0.0)
Sleep disorder NOS	0 (0.0)	2 (11.8)	0 (0.0)	1 (6.7)	0 (0.0)	2 (5.9)	0 (0.0)	1 (3.0)	0 (0.0)	1 (4.5)
Tension headaches	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (2.9)	0 (0.0)	2 (6.1)	0 (0.0)	1 (4.5)
Tinnitus	1 (5.9)	0 (0.0)	1 (6.3)	0 (0.0)	3 (16.7)	1 (2.9)	0 (0.0)	1 (3.0)	0 (0.0)	0 (0.0)
Osteoarthritis NOS	0 (0.0)	2 (11.8)	1 (6.3)	0 (0.0)	1 (5.6)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	1 (4.5)
Intervertebral disc herniation	2 (11.8)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Postoperative complications NOS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	2 (11.1)	0 (0.0)	0 (0.0)	1 (4.5)
Benign prostatic hyperplasia	1 (5.9)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)	0 (0.0)	0 (0.0)
Oesophagitis NOS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	2 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)

Cross-reference: Section 14.1, Table 10.4-4.1

TABLE 10.5A. Duration of Treatment with Oxycodone and Naloxone by Absolute Dose of Naloxone - Safety Population

	Absolute Dose of Naloxone			
	Naloxone Placebo	Naloxone 10 mg	Naloxone 20 mg	Naloxone 40 mg
Treatment	N=50 (100%)	N=51 (100%)	N=51 (100%)	N=50 (100%)
Oxycodone [days]				
Mean	48.1	44.0	45.7	44.2
SD	11.44	15.06	14.10	15.79
Median	50.0	49.0	49.0	49.0
Min-Max	6-61	7-62	9-70	7-63
Naloxone [days]				
Mean	25.4	24.1	25.1	23.3
SD	6.32	7.88	8.30	9.47
Median	27.0	27.0	27.0	27.0
Min-Max	1-30	0-30	0-41	0-30

Cross-reference: Section 14.1, Table 10.5-1.2

Note: Duration includes all days between first and last intake of medication as recorded in the patient diary

TABLE 10.5B. Duration of Treatment with Oxycodone and Naloxone by Oxycodone/Naloxone Dose Ratio - Safety Population

	Dose Ratios									
	40 mg/ Placebo	60 mg/ Placebo	80 mg/ Placebo	1/1	1.5/1	2/1	3/1	4/1	6/1	8/1
Treatment	N=17 (100%)	N=17 (100%)	N=16 (100%)	N=15 (100%)	N=18 (100%)	N=34 (100%)	N=18 (100%)	N=33 (100%)	N=12 (100%)	N=22 (100%)
Oxycodone [days]										
Mean	42.9	51.3	50.3	47.6	41.0	44.7	43.6	45.4	43.2	46.0
SD	16.31	4.18	8.84	11.11	17.64	16.07	17.42	12.77	16.18	14.34
Median	49.0	50.0	51.0	50.0	48.5	49.0	48.5	49.0	49.0	49.5
Min-Max	6-61	44-60	20-59	11-60	8-56	7-64	11-70	7-58	7-56	8-62
Naloxone [days]										
Mean	22.3	27.1	26.8	26.0	22.6	23.5	22.7	25.9	24.5	23.7
SD	9.79	1.34	3.80	6.24	10.51	9.08	12.01	5.84	7.70	8.27
Median	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	27.0	26.0
Min-Max	1-29	24-29	13-30	4-30	0-29	0-30	0-41	0-29	2-30	0-29

Cross-reference: Section 14.1, Table 10.5-1.1

Note: Duration includes all days between first and last intake of medication as recorded in the patient diary

10.6. Prior and Concomitant Medications

A glossary of prior and concomitant medication by ATC class and preferred term can be found in Table 10.6-4, Section 14.1. Details of prior medication are summarized by oxycodone/naloxone dose ratio, absolute dose of naloxone and by absolute dose of naloxone given the same oxycodone/naloxone dose ratio according to WHO ATC class and preferred term in Tables 10.6-1.1, 10.6-1.2 and 10.6-1.3, Section 14.1. Concomitant medication grouped by the dose ratio of oxycodone and naloxone is summarized by WHO ATC class in Table 10.6 (below) and in Tables 10.6-2.1, 10.6-2.2 and 10.6-2.3, Section 14.1, for oxycodone/naloxone dose ratio, absolute dose of naloxone and by absolute dose of naloxone given the same oxycodone/naloxone dose ratio. Prior and concomitant medications are presented in Listing 10.6-1, Appendix 16.2. Forbidden medication by oxycodone/naloxone dose ratio, absolute dose of naloxone and by absolute dose of naloxone given the same oxycodone/naloxone dose ratio is summarized in Tables 10.6-3.1, 10.6-3.2 and 10.6-3.3, Section 14.1 and presented by patient in Listing 10.6-2, Appendix 16.2.

As expected for the study population analgesics were the most commonly used prior medication (123 out of 202, 60.9%), followed by laxatives (103 out of 202, 51.0%) (Table 10.6-1.2, Section 14.1). Psychoanaleptics were also commonly used (82 out of 202 patients, 40.6%) (Table 10.6-1.2, Section 14.1) reflecting the relatively high incidence of concomitant depression (Table 10.4C). Antihypertensive agents including agents acting on the renin angiotensin system (34 patients, 16.8%), beta blocking agents (30 patients, 14.9%), diuretics (17 patients, 8.4%) and calcium channel blockers (18 patients, 8.9%) (Table 10.6-1.2, Section 14.1) also reflect the high incidence of hypertension as a prior or concomitant illness (Table 10.4C).

Laxatives were the most commonly used concomitant medication in each dose ratio and treatment group (191 out of 202 patients, 94.6%) with analgesics (85 out of 202, 42.1%) also frequently used (Table 10.6-2.2, Section 14.1). The high use of psychoanaleptics (87 out of 202, 43.1%) reflected the high diagnoses of depression in this population (Table 10.4C). The WHO ATC class analgesics included medication identified as forbidden. Fifty-six patients across all treatment groups in the safety population (27.7%) took forbidden medication (Table 10.6-3.2, Section 14.1). Forbidden medication included opioids other than oxycodone administered at the baseline visit. Only forbidden medications taken after the baseline visit were regarded as major protocol violations leading to exclusion from the PP population. Patients who were excluded from the PP population due to use of forbidden medication are provided in Listing 10.2-1, Appendix 16.2.

There were no relevant differences between the treatment groups or dose ratios concerning prior or concomitant medications.

TABLE 10.6B. Concomitant Medications by Oxycodone/Naloxone Dose Ratio (only medications reported for ≥15% of patients in any dose ratio group) and Therapeutic Class - Safety Population

	Dose Ratios									
WHO ATC Class	40 mg/ Placebo N=17 (100%)	60 mg/ Placebo N=17 (100%)	80 mg/ Placebo N=16 (100%)	1/1 N=15 (100%)	1.5/1 N=18 (100%)	2/1 N=34 (100%)	3/1 N=18 (100%)	4/1 N=33 (100%)	6/1 N=12 (100%)	8/1 N=22 (100%)
Laxatives	15 (88.2)	16 (94.1)	15 (93.8)	14 (93.3)	17 (94.4)	33 (97.1)	18 (100.0)	31 (93.9)	12 (100.0)	20 (90.9)
Psychoanaleptics	7 (41.2)	7 (41.2)	7 (43.8)	7 (46.7)	6 (33.3)	12 (35.3)	9 (50.0)	16 (48.5)	4 (33.3)	12 (54.5)
Analgesics	7 (41.2)	8 (47.1)	8 (50.0)	6 (40.0)	7 (38.9)	11 (32.4)	6 (33.3)	14 (42.4)	6 (50.0)	12 (54.5)
Antiinflammatory and antirheumatic products	7 (41.2)	3 (17.6)	2 (12.5)	6 (40.0)	7 (38.9)	13 (38.2)	3 (16.7)	11 (33.3)	4 (33.3)	9 (40.9)
Antispasmodics and anticholinergic agents and propulsives	4 (23.5)	5 (29.4)	4 (25.0)	4 (26.7)	3 (16.7)	7 (20.6)	4 (22.2)	8 (24.2)	4 (33.3)	4 (18.2)
Agents acting on the renin-angiotensin system	2 (11.8)	1 (5.9)	2 (12.5)	4 (26.7)	3 (16.7)	4 (11.8)	4 (22.2)	7 (21.2)	1 (8.3)	6 (27.3)
Antiepileptics	3 (17.6)	4 (23.5)	5 (31.3)	3 (20.0)	1 (5.6)	5 (14.7)	7 (38.9)	1 (3.0)	1 (8.3)	2 (9.1)
Antacids, drugs for treatment of peptic ulcers and flatulence	2 (11.8)	2 (11.8)	1 (6.3)	1 (6.7)	5 (27.8)	3 (8.8)	4 (22.2)	7 (21.2)	1 (8.3)	3 (13.6)
Beta blocking agents	2 (11.8)	2 (11.8)	2 (12.5)	2 (13.3)	2 (11.1)	1 (2.9)	3 (16.7)	7 (21.2)	1 (8.3)	7 (31.8)
Antithrombotic agents	1 (5.9)	2 (11.8)	2 (12.5)	0 (0.0)	2 (11.1)	4 (11.8)	2 (11.1)	7 (21.2)	1 (8.3)	3 (13.6)
Thyroid therapy	2 (11.8)	3 (17.6)	1 (6.3)	2 (13.3)	2 (11.1)	7 (20.6)	1 (5.6)	3 (9.1)	0 (0.0)	2 (9.1)
Anesthetics	3 (17.6)	0 (0.0)	1 (6.3)	0 (0.0)	2 (11.1)	2 (5.9)	3 (16.7)	6 (18.2)	1 (8.3)	2 (9.1)
Serum lipid reducing agents	0 (0.0)	1 (5.9)	0 (0.0)	1 (6.7)	5 (27.8)	3 (8.8)	2 (11.1)	6 (18.2)	0 (0.0)	2 (9.1)
Diuretics	1 (5.9)	1 (5.9)	0 (0.0)	0 (0.0)	2 (11.1)	1 (2.9)	2 (11.1)	4 (12.1)	1 (8.3)	7 (31.8)
Vitamins	2 (11.8)	2 (11.8)	2 (12.5)	1 (6.7)	3 (16.7)	0 (0.0)	2 (11.1)	4 (12.1)	1 (8.3)	1 (4.5)
Antihistamines for systemic use	2 (11.8)	3 (17.6)	1 (6.3)	1 (6.7)	1 (5.6)	1 (2.9)	1 (5.6)	4 (12.1)	1 (8.3)	1 (4.5)
Muscle relaxants	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)	4 (11.8)	1 (5.6)	5 (15.2)	1 (8.3)	1 (4.5)
Cardiac therapy	0 (0.0)	1 (5.9)	1 (6.3)	0 (0.0)	3 (16.7)	1 (2.9)	2 (11.1)	2 (6.1)	0 (0.0)	3 (13.6)
Urologicals	1 (5.9)	2 (11.8)	1 (6.3)	0 (0.0)	3 (16.7)	0 (0.0)	1 (5.6)	1 (3.0)	0 (0.0)	1 (4.5)

Cross-reference: Section 14.1, Table 10.6-2.1
Note: Concomitant medication includes all medication administered at or after the day of the baseline visit

added to patients' treatment regimen) and the end of the maintenance phase for the absolute dose of naloxone groups (Table 11.1.1.1B, below) or dose ratio groups (Table 11.1.1.1A, below).

Analyzed by absolute naloxone dose (10 mg, 20 mg or 40 mg), mean pain intensity ranged from 38.3 (±18.49) to 38.8 (±16.59) compared to 36.9 (±15.74) for placebo during the last 7 days prior to Visit 4 and 37.2 (±17.24) to 38.7 (±17.05) compared to 37.8 (±18.22) for placebo during the last 7 days at the end of the maintenance phase (Table 11.1.1.1B, below). The differences between naloxone placebo treatment and the 10 mg, 20 mg and 40 mg naloxone treatments were small, with the 90%confidence intervals for the differences in Table 11.1.1.1D (below) being narrow relative to the 0 to 100 pain scale. Hence, the data did not indicate a negative effect of naloxone on the analgesic efficacy of oxycodone. The 90% confidence intervals for the differences based on an ANCOVA test with Visit 3 pain as covariate ((-3.8, 4.3), (-6.5, 1.6) and (-4.2, 3.9) for 10mg, 20mg and 40mg naloxone, respectively, versus placebo - Table 12.8-2.5 , Section 14.2) were similarly narrow.

At randomization mean (±SD) pain intensity ranged from 33.2 (±12.92) to 41.3 (±19.68) for the dose ratios. During the last 7 days of the maintenance phase mean (±SD) pain intensity ranged from 33.9 (±17.71) to 42.1 (±22.48) for all oxycodone/naloxone dose ratios and from 36.8 (±17.83) to 38.7 (±20.80) for all oxycodone/naloxone placebo dose ratios. Similar values were seen during the last 7 days prior to Visit 4 (first visit of treatment period) when mean (±SD) pain intensity ranged from 34.1 (±12.25) to 41.3 (±20.86) for the dose ratio groups.

Identical dose ratios were obtained for 40 mg oxycodone/10 mg naloxone and 80 mg oxycodone/20 mg naloxone (4/1) and for 40 mg oxycodone/20 mg naloxone and 80 mg oxycodone/40 mg naloxone (2/1). Analysis by absolute dose of naloxone given the same oxycodone/naloxone dose ratio showed that within the 4/1 dose ratio group during the last 7 days at the end of the maintenance phase, mean pain intensity (±SD) of those patients taking 10 mg naloxone (40/10) was 33.5 (±22.13) and 49.1 (±20.88) for those taking 20 mg naloxone (80/20). In the 2/1 dose ratio group the values were 25.8 (±16.03) for those taking 20 mg naloxone (40/20) and 43.3 (±15.11) for those taking 40 mg naloxone (80/40). For both dose ratios, patients taking the higher naloxone and oxycodone dose recorded higher mean pain intensity scores at Visits 3, 4 and 5 (Table 11.1.1.1D below).

There was no major change in mean pain intensity from the end of the maintenance phase to the end of follow-up when patients were receiving oxycodone alone for the dose ratio groups (Table 11.1.1.1A, below) or the treatment groups (Table 11.1.1.1B, below).

The trends observed in the ITT population were generally mirrored by the results of the PP analysis for the intensity of mean pain. At the end of the maintenance phase, mean pain for all oxycodone/naloxone dose ratios ranged from 31.1 (±18.51) to 42.5 (±21.43) compared to 25.6 (±17.18) to 36.7 (±19.03) in the oxycodone/placebo dose ratios. At the end of the maintenance phase mean pain ranged from 36.1 (±19.47) to 38.9 (±18.83) for 10, 20 and 40 mg naloxone compared to 32.6 (±16.56) for patients taking naloxone placebo. Similar values were recorded at Visit 4. At randomization, there was a numerical imbalance in the mean pain intensity by naloxone dose group: 34.0 for naloxone placebo, 38.0 for 10mg, 40.1 for 20mg and 39.0 for 40mg naloxone (Table 12.8-1.4, Section 14.2). In light of this imbalance, an additional analysis of the pain intensity data using ANCOVA with baseline pain intensity as covariate, was performed and the results are considered more relevant than the ANOVA results. The 90% confidence intervals for the Visit 5 differences based on an ANCOVA test with Visit 3 average pain as covariate ((-2.0, 8.2), (-6.7, 4.0) and (-3.3, 7.4) for 10mg, 20mg and 40mg naloxone, respectively, versus placebo - Table 12.8 - 2.13 , Section 14.2) were similarly narrow with respect to the 0 to 100 pain scale and did not indicate a naloxone effect on analgesic efficacy.

TABLE 11.1.1.1A. Mean Pain at Each Study Visit by Oxycodone/Naloxone Dose Ratio - ITT Population with Non-missing Values

				Dose Ratios						
Average Pain Intensity (NAS)	40 mg/ Placebo N=17 (100%)	60 mg/ Placebo N=17 (100%)	80 mg/ Placebo N=16 (100%)	1/1 N=15 (100%)	1.5/1 N=17 (100%)	2/1 N=32 (100%)	3/1 N=17 (100%)	4/1 N=32 (100%)	6/1 N=11 (100%)	8/1 N=22 (100%)
Visit 2 (Baseline)*										
N	17	17	16	15	17	32	17	32	11	22
Mean	41.5	54.8	53.8	41.3	49.4	48.6	55.0	50.9	49.5	58.4
SD	15.69	23.66	21.02	18.56	18.78	20.10	9.01	22.20	17.39	19.66
Median	40.0	60.0	55.0	40.0	50.0	50.0	50.0	50.0	50.0	60.0
Min-Max	20-70	20-100	0-80	15-70	20-80	10-80	40-70	10-100	30-80	20-100
Visit 3 (Randomization)**										
N	17	17	16	15	17	32	17	32	11	22
Mean	40.5	33.2	38.6	35.8	33.8	37.1	40.6	41.3	38.0	40.4
SD	14.64	12.92	19.39	16.30	13.67	16.93	15.61	19.68	14.07	15.40
Median	38.6	31.4	43.6	34.3	30.0	36.6	43.3	41.6	36.9	41.6
Min-Max	12-62	8-58	0-62	18-67	15-61	10-73	8-72	1-81	18-64	13-63
Visit 4 (Maintenance)**										
N	15	17	16	15	15	28	16	31	11	21
Mean	38.5	34.1	38.3	39.7	34.6	36.0	39.5	41.3	38.0	39.6
SD	14.38	12.25	20.24	16.37	17.30	17.45	16.08	20.86	14.84	14.32
Median	33.6	30.0	36.4	35.0	33.8	35.7	41.4	40.8	37.1	38.9
Min-Max	10-60	16-56	6-66	20-74	7-72	3-73	0-69	7-84	10-63	19-66
Visit 5 (End of Maintenance)**										
N	14	17	15	14	14	28	12	29	10	19
Mean	38.0	36.8	38.7	38.9	34.4	33.9	36.7	42.1	35.1	40.9
SD	17.03	17.83	20.80	17.15	18.65	17.71	17.30	22.48	15.87	14.04
Median	42.9	31.1	36.7	34.5	35.1	32.9	38.9	38.2	34.4	36.1
Min-Max	9-61	16-78	0-71	20-79	10-75	3-69	2-66	5-98	3-58	17-68
Visit 6 (End of Follow-up)**										
N	13	17	15	13	13	25	12	28	9	18
Mean	37.5	34.9	43.3	38.3	31.7	30.9	36.5	41.8	36.2	37.4
SD	14.43	14.26	21.64	22.16	13.18	18.68	17.61	21.83	18.07	15.77
Median	35.7	30.0	42.9	32.1	30.7	26.8	38.4	43.6	40.7	36.3
Min-Max	14-66	18-69	0-75	13-76	14-53	0-72	1-65	7-92	4-57	2-62

Cross-reference: Section 14.2, Table 11.1.1.1-1.1a

Note: NAS (0 = no pain, 100 = worst imaginable pain); *Average pain intensity during the last 7 days according to patient assessment; **Average pain intensity for all values recorded during the last 7 days according to patient diary

TABLE 11.1.1.1C. Mean Pain at Each Study Visit by Absolute Dose of Naloxone Given the Same Oxycodone/Naloxone Dose Ratio - ITT Population with Non-missing Values

	Dose ratio			
Average Pain Intensity (NAS)	4/1 10 mg naloxone N=16 (100%)	4/1 20 mg naloxone N=16 (100%)	2/1 20 mg naloxone N=16 (100%)	2/1 40 mg naloxone N=16 (100%)
Visit 2 (Baseline)*				
N	16	16	16	16
Mean	44.1	57.8	46.3	50.9
SD	24.91	17.22	21.17	19.38
Median	37.5	57.5	45.0	50.0
Min-Max	10-100	30-90	15-80	10-80
Visit 3 (Randomization)**				
N	16	16	16	16
Mean	37.3	45.4	31.4	42.8
SD	21.19	17.78	17.62	14.57
Median	41.2	41.8	28.6	41.2
Min-Max	1-63	16-81	10-73	10-66
Visit 4 (Maintenance)**				
N	15	16	15	13
Mean	37.7	44.7	30.3	42.5
SD	21.51	20.32	16.96	16.21
Median	40.8	39.9	31.8	42.9
Min-Max	7-65	16-84	3-73	16-67
Visit 5 (End of Maintenance)**				
N	13	16	15	13
Mean	33.5	49.1	25.8	43.3
SD	22.13	20.88	16.03	15.11
Median	35.0	42.3	26.7	42.5
Min-Max	5-74	22-98	3-69	11-69
Visit 6 (End of Follow-up)**				
N	13	15	14	11
Mean	33.7	48.7	25.1	38.3
SD	20.78	20.91	18.55	16.77
Median	35.0	45.0	22.1	35.7
Min-Max	7-67	19-92	0-72	10-70

Cross-reference: Section 14.2, Table 11.1.1.1-1.3a

Note: NAS (0 = no pain, 100 = worst imaginable pain); *Average pain intensity during the last 7 days according to patient assessment; **Average pain intensity for all values recorded during the last 7 days according to patient diary

Mean Pain – Per Protocol Population (PP) – Not Adjusted for Baseline			
Mean pain intensity during the last 7 days at Visit 5 (end of maintenance)			
N in test group	26	22	22
N in placebo group	29	29	29
Difference in means*	6.3	3.6	5.1
90% CI	(-1.6, 14.2)	(-4.9, 12.0)	(-1.8, 13.9)
P-value**	0.359	0.193	0.341
Mean Pain – Per Protocol Population (PP) – Adjusted for Baseline			
Mean pain intensity during the last 7 days at Visit 5 (end of maintenance)			
N in test group	26	22	22
N in placebo group	29	29	29
Difference in means#	3.1	-1.3	2.1
90% CI	(-2.0, 8.2)	(-6.7, 4.0)	(-3.3, 7.4)
P-value##	0.056	0.002	0.035

Cross-reference: Section 14.2, Table 11.1.1.1-2a, Table 11.1.1.1-2b, Table 12.8-2.5 and Table 12.8-2.13
Note: NAS (0 = no pain, 100 = worst imaginable pain); *Mean in test group minus mean in placebo group; **One sided t-test for non-inferiority with equivalence limit 8; #Least square mean test group minus placebo group (adjusted by values of Visit 3); ## One sided t-test for non-inferiority with equivalence limit 8 (adjusted by values of Visit 3)

During the last 7 days at the end of the maintenance phase, mean (±SD) bowel function was lowest in the 1/1, 1.5/1 and 2/1 dose ratios (21.9±22.25, 21.8±21.35 and 26.7±23.98 for the 1/1, 1.5/1 and 2/1 dose ratios, respectively). Furthermore, mean bowel function worsened as the amount of naloxone decreased, to a maximum value of 47.8 (±23.20) for a dose ratio of 6/1. For the last 7 days prior to Visit 4, mean bowel function ranged from 20.7 (±19.24) at a ratio of 1/1 to 45.7 (±26.86) at a ratio of 8/1 (Table 11.1.1.2A, below). Values for mean bowel function in the oxycodone/naloxone placebo dose ratios were higher than in the 1/1, 1.5/1 and 2/1 dose ratios at both visits.

Analysis by absolute dose of naloxone given the same oxycodone/naloxone dose ratio showed that within both dose ratio groups (4/1 and 2/1) patients taking the higher oxycodone dose had higher mean bowel function values at Visits 3, 4 and 5 (Table 11.1.1.2C, below).

From the end of the maintenance phase to end of follow-up, mean bowel function worsened (Tables 11.1.1.2-1a, 11.1.1.2-1.2a and 11.1.1.2-1.3a, Section 14.2). The range for mean bowel function was 21.8 (±21.35) to 48.2 (±21.71) for the dose ratio groups at end of maintenance and 33.2 (±20.76) to 52.1 (±26.79) for the dose ratio groups at the end of follow-up (Table 11.1.1.2-1.1a, Section 14.2). The change was greatest in the 40 mg naloxone group; mean bowel function was 26.1 (±25.08) at the end of maintenance and 42.4 (±23.19) at the end of follow-up (Table 11.1.1.2-1.2a, Section 14.2).

Analysis using the PP population generally mirrored the trends observed in the ITT population with regards to mean bowel function. During the last 7 days at the end of the maintenance phase, mean (±SD) bowel function was lowest in the 1/1 dose ratio (10.7±15.35) and worsened to a maximum of 57.3 (±17.38) for a dose ratio of 6/1. Mean bowel function values were higher than the 1/1, 1.5/1 and 2/1 ratios for all oxycodone/placebo dose ratios (Table 11.1.1.2-1b, Section 14.2). Similar values were seen for the last 7 days prior to Visit 4 with the exception of the 3/1 dose ratio. At the end of the maintenance phase mean bowel function was 42.3 (±24.03), 39.4 (±23.44), 29.8 (±29.29) and 29.6 (±28.34) for placebo, 10 mg, 20 mg and 40 mg naloxone (Table 11.1.1.2-1.2b, Section 14.2). The small number of patients in each treatment group in the PP population meant statistically significant p-values were not obtained in the PP analysis for t-tests for difference for mean bowel function.

TABLE 11.1.1.2B. Mean Bowel Function at Each Study Visit by Absolute Dose of Naloxone - ITT Population with Non-missing Values

	Absolute Dose of Naloxone			
Average Bowel Function	Naloxone Placebo N=50 (100%)	Naloxone 10 mg N=49 (100%)	Naloxone 20 mg N=49 (100%)	Naloxone 40 mg N=48 (100%)
Visit 2 (Baseline)				
N	50	49	49	48
Mean	53.3	55.8	56.1	47.9
SD	23.28	19.81	20.19	19.65
Median	53.3	53.3	50.0	49.2
Min-Max	0-93	7-100	3-100	0-83
Visit 3 (Randomization)				
N	50	49	49	48
Mean	48.0	52.8	49.4	46.2
SD	23.97	22.86	22.72	20.67
Median	48.3	50.0	50.0	46.7
Min-Max	0-100	10-100	0-100	0-90
Visit 4 (Maintenance)				
N	48	47	47	42
Mean	43.3	42.1	34.2	27.9
SD	26.41	25.53	30.04	22.68
Median	46.7	40.0	30.0	28.3
Min-Max	0-93	0-100	0-100	0-73
Visit 5 (End of Maintenance)				
N	45	41	42	40
Mean	45.4	40.3	31.3	26.1
SD	22.28	23.09	25.82	25.08
Median	43.3	36.7	25.0	20.0
Min-Max	0-100	0-92	0-85	0-90
Visit 6 (End of Follow-up)				
N	45	41	41	39
Mean	49.0	45.1	46.4	42.4
SD	25.01	23.72	26.98	23.19
Median	50.0	50.0	43.3	40.0
Min-Max	0-100	0-80	0-100	0-80

Cross-reference: Section 14.2, Table 11.1.1.2-1.2a
Note: Average bowel function = average of ease of defecation, feeling of incomplete bowel evacuation and judgment of constipation during the last 7 days according to patient assessment

TABLE 11.1.1.2D. Mean Bowel Function: Test for Difference Versus Placebo - ITT Populations

Category	Naloxone 10 mg vs Placebo	Naloxone 20 mg vs Placebo	Naloxone 40 mg vs Placebo
ITT Population with Non-missing Values			
Mean bowel function assessing the last 7 days at Visit 4			
N in test group	47	47	42
N in placebo group	48	48	48
Difference in means*	-1.2	-9.0	-15.4
95% CI	(-11.8, 9.4)	(-20.6, 2.5)	(-25.8, -5.0)
P-value**	0.827	0.122	0.004
Mean bowel function assessing the last 7 days at Visit 5 (end of maintenance)			
N in test group	41	42	40
N in placebo group	45	45	45
Difference in means*	-5.1	-14.1	-19.3
95% CI	(-14.9, 4.6)	(-24.4, -3.8)	(-29.5, -9.1)
P-value**	0.296	0.008	<0.001
LOCF ITT Population			
Mean bowel function assessing the last 7 days at Visit 5 (end of maintenance)			
N in test group	47	47	42
N in placebo group	48	48	48
Difference in means*	-6.7	-12.4	-18.2
95% CI	(-16.6, 3.1)	(-22.2, -2.5)	(-28.3, -8.0)
P-value**	0.180	0.014	0.001

Cross-reference: Section 14.2, Table 11.1.1.2-2a, Table 12.6-2.17

*Mean in test group minus mean in placebo group; **t-test for difference

In addition to estimating the treatment effect for individual oxycodone/naloxone combinations, overall treatment effect estimates were obtained for specific ratios. The estimates were calculated by combining the results from the different oxycodone/naloxone combinations, e.g.; the 2:1 ratio estimate was formed by averaging the predicted results of the 40/20 mg, 60/30 mg, and 80/40 mg oxycodone/naloxone combinations, relative to naloxone placebo. The estimated mean differences (SE) in mean bowel function for various oxycodone/naloxone ratios versus naloxone placebo groups are displayed below.

Table 11.1.1.1.2E: Response Surface Analysis of Bowel Function Efficacy by Oxycodone/Naloxone ratio (Estimated Improvement (SE) vs Naloxone Placebo)

Oxycodone/Naloxone Ratio	Overall Improvement (SE) vs Placebo
6:1	8.0 (3.3)
4:1	11.0 (4.1)
3:1	13.4 (4.6)
2:1	16.2 (4.5)
1.5:1	16.5 (5.1)

Cross reference: Section 14.2 Table 12.6-1.3

The estimates indicate that bowel function improvement increases as oxycodone/naloxone ratio decreases, with the estimated improvement at 2:1 approximately 50% higher than at 4:1 ($p<0.05$) and with a minimal improvement from the 2:1 ratio to the 1.5:1 ratio.

11.1.2. Secondary Efficacy Results

Descriptions of efficacy variables and analyses are presented in Sections 9.4.2 and 9.7.1.2. Complete listings of secondary efficacy data can be found in Listings 11.1.2-1 to 11.1.2-5, Appendix 16.2.

Secondary efficacy outcomes were: daily pain intensity, use of rescue medication, ease of defecation, feeling of incomplete bowel evacuation, judgment of constipation, stool frequency, stool consistency, laxative intake, mean laxative dose, and a global assessment of efficacy/tolerability/preference.

11.1.2.1. Daily Pain Intensity

Daily pain intensity is summarized in Tables 11.1.2.1-1, 11.1.2.1-2 and 11.1.2.1-3, Section 14.2 by oxycodone/naloxone dose ratio, absolute dose of naloxone and by absolute dose of naloxone given the same oxycodone/naloxone dose ratio for the ITT population. Pain intensity from the patient diary is in Listing 11.1.1-1b, Appendix 16.2. Figures 11.1.2.1-1, 11.1.2.1-2 and 11.1.2.1-3 (Section 14.2) show the course of daily pain intensity versus time during the maintenance phase, the titration phase and the follow-up phase respectively.

Figure 11.1.2.1 below shows the course of daily pain intensity through the maintenance phase.

Daily pain intensity was stable for all treatment groups throughout the course of the maintenance phase and no clear trends or apparent differences were seen in daily pain intensity between any absolute dose of naloxone treatment group (Figure 11.1.2.1). Furthermore, daily pain intensity by dose ratio showed a similar trend with a stable pain intensity maintained throughout the maintenance phase for each dose ratio (Table 11.1.2.1-1, Section 14.2). For daily pain intensity versus oxycodone dosing during the titration phase (Figure 11.1.2.1-2), the mean daily pain intensity declined and became stable over a 14 day period. After the maintenance phase and during follow-up, mean daily pain intensity remained generally stable and similar for the 40 mg and 60 mg oxycodone dose groups. A slight increase in the mean daily pain intensity was observed with 80 mg oxycodone during follow-up (Figure 11.1.2.1-3, Section 14.2).

Analyzed by absolute dose of naloxone given the same oxycodone/naloxone dose ratio, no major differences were apparent in the 2/1 ratio. In the 4/1 ratio there was a higher intake of rescue medication among those taking 20 mg naloxone (80/20) during the last 7 days prior to Visits 4 and 5: 4.3 (±6.54) compared to 0.5 (±0.92) in the 10 mg naloxone group (40/10) at the end of maintenance (Table 11.1.2.2-1.3, Section 14.2).

The mean amount (mg) of rescue medication during the last 7 days at the end of the maintenance phase were higher in the 10 mg and 20 mg naloxone groups. The values being 0.7±2.10, 2.5±7.76, 2.8±5.71, 0.8±1.95 for placebo, 10 mg, 20 mg and 40 mg naloxone respectively (Table 11.1.2.2B). A statistically significant difference ($p<0.05$) to placebo was obtained for the 10 mg and 20 mg naloxone groups, however, this difference was not considered to be of any clinical relevance. Statistically significant p-values were not obtained for any dose of naloxone versus placebo during the last 7 days prior to Visit 4 (Table 11.1.2.2-2, Section 14.2).

TABLE 11.1.2.2B. Rescue Medication at Each Study Visit by Absolute Dose of Naloxone - ITT Population with Non-missing Values

Mean Amount of Rescue Medication (mg per day)	Absolute Dose of Naloxone			
	Naloxone Placebo N=50 (100%)	Naloxone 10 mg N=49 (100%)	Naloxone 20 mg N=49 (100%)	Naloxone 40 mg N=48 (100%)
Visit 3 (Randomization)*				
N (n†)	50 (8)	49 (5)	49 (7)	48 (11)
Mean	1.2	1.4	0.8	1.7
SD	4.08	6.43	1.92	4.6
Median	0.0	0.0	0.0	0.0
Min-Max	0-20	0-43	0-9	0-20
Visit 4 (Maintenance)*				
N (n†)	48 (10)	47 (9)	47 (13)	43 (9)
Mean	1.8	1.0	2.3	1.3
SD	6.35	3.23	4.87	3.70
Median	0.0	0.0	0.0	0.0
Min-Max	0-40	0-20	0-20	0-20
Visit 5 (End of Maintenance)*				
N (n†)	46 (8)	42 (12)	43 (12)	41 (6)
Mean	0.7	2.5	2.8	0.8
SD	2.10	7.76	5.71	1.95
Median	0.0	0.0	0.0	0.0
Min-Max	0-12	0-46	0-20	0-7
Visit 6 (End of Follow-up)*				
N (n†)	45 (7)	40 (8)	41 (9)	37 (2)
Mean	2.5	1.1	1.8	0.2
SD	8.55	3.37	3.94	0.96
Median	0.0	0.0	0.0	0.0
Min-Max	0-40	0-20	0-15	0-6
Entire Maintenance Phase**				
N (n†)	50 (15)	49 (14)	49 (19)	47 (14)
Mean	0.9	1.6	2.1	1.4
SD	2.17	4.50	4.30	3.60
Median	0.0	0.0	0.0	0.0
Min-Max	0-10	0-24	0-19	0-20

Cross-reference: Section 14.2, Table 11.1.2.2-1.2

*Mean during the last 7 days according to patient diary; **Mean for all values recorded during maintenance phase according to patient diary

n† Number of patients taking rescue medication

TABLE 11.1.2.3A. Ease of Defecation at Each Study Visit by Oxycodone/Naloxone Dose Ratio - ITT Population with Non-missing Values

	Dose Ratios									
Ease of Defecation (NAS)	40 mg/ Placebo N=17 (100%)	60 mg/ Placebo N=17 (100%)	80 mg/ Placebo N=16 (100%)	1/1 N=15 (100%)	1.5/1 N=17 (100%)	2/1 N=32 (100%)	3/1 N=17 (100%)	4/1 N=32 (100%)	6/1 N=11 (100%)	8/1 N=22 (100%)
Visit 2 (Baseline)*										
N	17	17	16	15	17	32	17	32	11	22
Mean	57.9	49.7	63.1	50.7	54.7	57.0	58.2	56.4	57.3	66.4
SD	24.94	26.13	17.78	16.24	19.40	26.79	24.55	23.18	20.54	17.33
Median	60.0	50.0	65.0	50.0	50.0	60.0	60.0	52.5	50.0	70.0
Min-Max	0-100	0-80	30-90	20-80	20-90	0-100	0-100	10-100	30-100	30-100
Visit 3 (Randomization)*										
N	17	17	16	15	17	32	17	32	11	22
Mean	49.7	48.5	59.4	46.7	56.5	50.8	42.9	55.9	58.2	64.1
SD	24.65	34.54	16.52	19.88	24.73	25.02	22.01	25.19	25.23	20.22
Median	50.0	50.0	55.0	40.0	50.0	55.0	40.0	50.0	70.0	70.0
Min-Max	0-100	0-100	30-80	20-90	0-90	0-100	0-80	10-100	20-100	30-100
Visit 4 (Maintenance)*										
N	15	17	16	15	14	28	16	31	11	21
Mean	49.0	50.0	47.5	24.7	23.6	40.2	27.5	43.4	47.3	47.6
SD	25.51	35.13	31.30	24.75	17.37	26.54	34.35	27.58	30.03	26.20
Median	50.0	60.0	50.0	20.0	25.0	40.0	15.0	40.0	50.0	50.0
Min-Max	0-100	0-100	0-100	0-60	0-50	0-80	0-100	0-100	0-90	0-100
Visit 5 (End of Maintenance)*										
N	13	17	15	14	14	27	12	27	10	19
Mean	48.5	49.4	54.0	25.7	24.3	27.6	35.8	42.7	50.0	45.0
SD	24.10	27.55	23.54	26.81	23.69	24.86	28.11	25.33	24.94	27.89
Median	50.0	50.0	50.0	20.0	22.5	25.0	30.0	40.0	55.0	50.0
Min-Max	10-100	0-100	0-90	0-70	0-70	0-90	0-80	0-90	10-80	0-95
Visit 6 (End of Follow-up)*										
N	13	16	15	14	13	26	12	28	10	18
Mean	58.8	48.1	50.0	37.9	54.6	48.1	55.0	55.9	52.0	50.0
SD	25.83	25.94	31.40	21.90	26.96	29.53	36.31	23.92	23.94	27.39
Median	50.0	50.0	50.0	40.0	60.0	50.0	50.0	50.0	50.0	50.0
Min-Max	10-100	0-90	0-100	0-80	0-80	0-100	0-100	0-100	10-80	0-90

Cross-reference: Section 14.2, Table 11.1.2.3-1.1

Note: NAS (0 = easy/no difficulty, 100 = severe difficulty); *Mean during the last 7 days according to patient assessment

11.1.2.4. Feeling of Incomplete Bowel Evacuation

Feeling of incomplete bowel evacuation (ITT population) by oxycodone/naloxone dose ratio, absolute dose of naloxone and by absolute dose of naloxone given the same oxycodone/naloxone dose ratio is presented in Tables 11.1.2.4-1.1, 11.1.2.4-1.2 and 11.1.2.4-1.3 (Section 14.2). The test for difference between each dose of naloxone and placebo is summarized in Table 11.1.2.4-2 (Section 14.2). Bowel function assessment including the individual measures of ease of defecation, feeling of incomplete bowel evacuation and judgment of constipation and mean bowel function by patient is provided in Listing 11.1.2-1, Appendix 16.2.

Feeling of incomplete bowel evacuation at each study visit by oxycodone/naloxone dose ratio and by absolute dose of naloxone is summarized in Table 11.1.2.4A and 11.1.2.4B below.

Improvements in feeling of incomplete bowel evacuation were seen during the last 7 days at the end of the maintenance phase and during the last 7 days prior to Visit 4 as the dose of naloxone increased (Table 11.1.2.4B). The mean (±SD) values at the end of the maintenance phase were 36.0 (±29.19), 33.5 (±26.37), 27.5 (±26.53), 23.6 (±25.11) for placebo, 10 mg, 20 mg and 40 mg naloxone ($p<0.05$ for 20 mg and 40 mg naloxone versus placebo, Table 11.1.2.4-2, Section 14.2). An absolute dose of naloxone of 40 mg was statistically different from placebo at both Visits 4 and 5 ($p<0.05$) (Table 11.1.2.4-2, Section 14.2).

The lowest mean values for feeling of incomplete bowel evacuation were reported at dose ratios of 1/1 and 1.5/1 at both end of maintenance (17.9±21.19 and 18.9±22.38 respectively) and Visit 4 (17.3±17.92 and 23.2±19.38 respectively) and at the dose ratio 2/1 at the end of maintenance (26.1±23.79) and 3/1 at Visit 4 (21.9±33.31). The highest mean value for feeling of incomplete bowel evacuation at the end of maintenance (45.0±23.21) was recorded for the 6/1 dose ratio group (Table 11.1.2.4A).

Analysis by absolute dose of naloxone given the same oxycodone/naloxone dose ratio shows that within both dose ratio groups (4/1 and 2/1) patients taking the higher naloxone dose had higher mean values of feeling of incomplete bowel evacuation at Visit 4 and end of maintenance. However, those patients taking 40 mg oxycodone with either 10 mg naloxone (4/1) or 20 mg naloxone (2/1) had lower mean values than the alternate dose of oxycodone (80 mg) at Visit 4 and end of maintenance (Table 11.1.2.4-1.3, Section 14.2).

Mean values for feeling of incomplete bowel evacuation increased from the end of maintenance to end of follow-up for all naloxone ratios (except the 3/1 ratio) and treatment groups.

These trends are in agreement with those seen for ease of defecation.

TABLE 11.1.2.4B. Feeling of Incomplete Bowel Evacuation at Each Study Visit by Absolute Dose of Naloxone - ITT Population with Non-missing Values

Feeling of Incomplete Bowel Evacuation (NAS)	Absolute Dose of Naloxone			
	Naloxone Placebo N=50 (100%)	Naloxone 10 mg N=49 (100%)	Naloxone 20 mg N=49 (100%)	Naloxone 40 mg N=48 (100%)
Visit 2 (Baseline)*				
N	50	49	49	48
Mean	45.9	50.8	47.9	40.1
SD	29.08	21.90	25.52	25.36
Median	50.0	50.0	50.0	40.0
Min-Max	0-100	0-100	0-100	0-90
Visit 3 (Randomization)*				
N	50	49	49	48
Mean	40.6	44.4	43.7	37.3
SD	30.06	30.62	26.98	26.88
Median	40.0	50.0	50.0	40.0
Min-Max	0-100	0-100	0-100	0-90
Visit 4 (Maintenance)*				
N	48	47	47	42
Mean	34.6	38.6	31.6	25.8
SD	31.42	28.30	31.76	23.48
Median	35.0	40.0	20.0	20.0
Min-Max	0-100	0-100	0-100	0-70
Visit 5 (End of Maintenance)*				
N	45	41	42	40
Mean	36.0	33.5	27.5	23.6
SD	29.19	26.37	26.53	25.11
Median	30.0	40.0	20.0	15.0
Min-Max	0-100	0-90	0-80	0-90
Visit 6 (End of Follow-up)*				
N	44	41	41	39
Mean	40.8	36.7	35.6	34.0
SD	27.87	27.24	30.52	25.45
Median	50.0	50.0	30.0	40.0
Min-Max	0-100	0-80	0-100	0-80

Cross-reference: Section 14.2, Table 11.1.2.4-1.2
Note: NAS (0 = not at all, 100 = very strong); *Mean during the last 7 days according to patient assessment

TABLE 11.1.2.5A. Judgment of Constipation at Each Study Visit by Oxycodone/Naloxone Dose Ratio - ITT Population with Non-missing Values

				Dose Ratios						
Judgment of Constipation (NAS)	40 mg/ Placebo N=17 (100%)	60 mg/ Placebo N=17 (100%)	80 mg/ Placebo N=16 (100%)	1/1 N=15 (100%)	1.5/1 N=17 (100%)	2/1 N=32 (100%)	3/1 N=17 (100%)	4/1 N=32 (100%)	6/1 N=11 (100%)	8/1 N=22 (100%)
Visit 2 (Baseline)*										
N	17	17	16	15	17	32	17	32	11	22
Mean	55.6	50.6	65.6	45.3	51.8	56.6	59.4	57.5	55.5	61.4
SD	26.33	29.68	21.90	13.56	17.04	23.19	23.04	25.24	19.16	22.10
Median	60.0	50.0	65.0	50.0	50.0	60.0	50.0	57.5	50.0	65.0
Min-Max	0-100	0-100	40-100	30-80	20-80	0-95	30-100	0-100	30-100	0-90
Visit 3 (Randomization)*										
N	17	17	16	15	17	32	17	32	11	22
Mean	45.6	44.7	63.1	44.0	50.9	51.4	44.1	54.6	58.4	65.2
SD	27.49	26.90	17.78	18.44	23.33	22.69	28.74	25.47	24.20	21.07
Median	40.0	40.0	65.0	40.0	50.0	55.0	40.0	56.0	60.0	70.0
Min-Max	0-100	0-80	30-90	20-90	0-90	0-90	0-100	0-100	20-100	20-100
Visit 4 (Maintenance)*										
N	15	17	16	15	14	28	16	31	11	21
Mean	42.7	52.1	43.8	20.0	20.0	35.2	26.3	42.7	43.6	46.2
SD	26.04	30.42	29.86	18.80	19.22	25.51	33.44	29.83	25.80	30.29
Median	40.0	60.0	50.0	20.0	15.0	30.0	15.0	40.0	50.0	40.0
Min-Max	0-80	0-100	0-90	0-50	0-60	0-70	0-100	0-100	0-80	0-100
Visit 5 (End of Maintenance)*										
N	13	17	15	14	14	27	12	27	10	19
Mean	48.5	46.2	54.7	22.1	22.1	26.5	38.3	41.1	48.5	41.8
SD	24.44	29.34	23.86	22.25	23.92	25.71	30.70	31.63	24.04	29.96
Median	40.0	40.0	50.0	20.0	10.0	20.0	30.0	30.0	47.5	50.0
Min-Max	10-100	0-100	0-90	0-70	0-70	0-90	0-80	0-100	10-80	0-90
Visit 6 (End of Follow-up)*										
N	13	17	15	14	13	26	12	28	10	18
Mean	54.2	48.8	54.7	34.3	51.2	46.2	46.7	55.2	50.0	46.9
SD	28.57	27.07	28.00	20.27	24.85	28.72	31.43	26.33	22.11	29.86
Median	50.0	50.0	60.0	40.0	60.0	45.0	45.0	50.0	50.0	50.0
Min-Max	0-100	0-90	0-100	0-80	0-80	0-100	0-100	0-100	10-80	0-90

Cross-reference: Section 14.2, Table 11.1.2.5-1.1
Note: NAS (0 = not at all, 100 = very strong); *Mean during the last 7 days according to patient assessment

11.1.2.6. Stool Frequency

Stool frequency (ITT population) is presented in Tables 11.1.2.6-1.1, 11.1.2.6-1.2 and 11.1.2.6-1.3 (Section 14.2) by oxycodone/naloxone dose ratio, absolute dose of naloxone and by absolute dose of naloxone given the same oxycodone/naloxone dose ratio. Table 11.1.2.6-2 (Section 14.2) presents the test for difference between each dose of naloxone and placebo. Stool frequency and stool consistency by patient from the patient diary is provided in Listing 11.1.2-2, Appendix 16.2.

Mean stool frequency (per day) at each study visit by oxycodone/naloxone dose ratio and by absolute dose of naloxone is summarized in Table 11.1.2.6A and 11.1.2.6B below.

For each treatment group there was a trend towards an increase in stool frequency with increasing dose of naloxone during the last 7 days prior to Visit 4, the mean (±SD) values being 0.9 (±0.46), 1.0 (±0.48), 1.2 (±0.82), 1.4 (±0.63) for placebo, 10 mg, 20 mg and 40 mg respectively (Table 11.1.2.6B) ($p<0.001$ for 40 mg versus placebo). A similar, but weaker trend was observed at the end of the maintenance phase with a statistically significant difference to placebo ($p<0.05$) recorded for 40 mg naloxone at the end of the maintenance phase (Table 11.1.2.6-2, Section 14.2).

Mean (±SD) stool frequency values had a narrow range among the dose ratio groups during the entire maintenance phase. For the last 7 days prior to Visit 4 and the end of the maintenance phase, the lowest mean values of stool frequency were recorded for the 60 mg oxycodone/placebo, 80 mg oxycodone/placebo, 4/1 and 8/1 dose ratios and the highest for the 1/1 and 1.5/1 dose ratios (0.8±0.49, 0.8±0.25, 0.9±0.35, 0.9±0.35, 1.2±0.65 and 1.3±0.59 for 60 mg oxycodone/placebo, 80 mg oxycodone/placebo, 4/1, 8/1, 1/1 and 1.5/1 dose ratios respectively at the end of the maintenance phase) (Table 11.1.2.6A below). Moreover, mean stool frequency was consistently higher in the 1/1 and 1.5/1 dose ratios than for any placebo group at both visits.

Analysis by absolute dose of naloxone given the same oxycodone/naloxone dose ratio shows no identifiable differences between the absolute dose of naloxone within either dose ratio group (4/1 and 2/1) (Table 11.1.2.6-1.3, Section 14.2).

TABLE 11.1.2.6B. Stool Frequency at Each Study Visit by Absolute Dose of Naloxone - ITT Population with Non-missing Values

	Absolute Dose of Naloxone			
Mean Stool Frequency (per day)	Naloxone Placebo N=50 (100%)	Naloxone 10 mg N=49 (100%)	Naloxone 20 mg N=49 (100%)	Naloxone 40 mg N=48 (100%)
Visit 3 (Randomization)*				
N	50	49	49	48
Mean	1.0	1.0	0.9	1.0
SD	0.52	0.59	0.50	0.47
Median	1.0	1.0	0.9	1.0
Min-Max	0-2	0-4	0-3	0-2
Visit 4 (Maintenance)*				
N	48	47	47	43
Mean	0.9	1.0	1.2	1.4
SD	0.46	0.48	0.82	0.63
Median	0.8	1.0	1.0	1.3
Min-Max	0-2	0-3	0-6	0-3
Visit 5 (End of Maintenance)*				
N	46	42	43	42
Mean	0.9	1.0	1.0	1.1
SD	0.46	0.48	0.45	0.59
Median	0.9	1.0	1.0	1.0
Min-Max	0-2	0-3	0-2	0-3
Visit 6 (End of Follow-up)*				
N	45	41	41	39
Mean	0.9	0.9	0.9	0.9
SD	0.42	0.45	0.38	0.50
Median	0.9	0.9	0.9	1.0
Min-Max	0-2	0-2	0-2	0-2
Entire Maintenance Phase**				
N	50	49	49	47
Mean	1.0	1.0	1.2	1.3
SD	0.47	0.42	0.76	0.67
Median	0.9	0.9	1.0	1.1
Min-Max	0-2	0-3	0-5	0-3

Cross-reference: Section 14.2, Table 11.1.2.6-1.2
*Mean during the last 7 days according to patient diary; **Mean for all values recorded during maintenance phase according to patient diary

TABLE 11.1.2.7A. Stool Consistency During the Maintenance Phase by Oxycodone/Naloxone Dose Ratio - ITT Population with Non-missing Values

Median Stool Consistency During the Maintenance Phase	Dose Ratios									
	40 mg/ Placebo	60 mg/ Placebo	80 mg/ Placebo	1/1	1.5/1	2/1	3/1	4/1	6/1	8/1
	N=17 (100%)	N=17 (100%)	N=16 (100%)	N=15 (100%)	N=17 (100%)	N=32 (100%)	N=17 (100%)	N=32 (100%)	N=11 (100%)	N=22 (100%)
Entire Maintenance Phase*										
N (%)	17 (100)	17 (100)	16 (100)	15 (100)	17 (100)	31 (100)	17 (100)	32 (100)	11 (100)	21 (100)
Hard (%)	2 (11.8)	2 (11.8)	0 (0.0)	1 (6.7)	0 (0.0)	2 (6.5)	0 (0.0)	4 (12.5)	1 (9.1)	3 (14.3)
Solid (%)	3 (17.6)	3 (17.6)	5 (31.3)	4 (26.7)	2 (11.8)	7 (22.6)	4 (23.5)	7 (21.9)	3 (27.3)	8 (38.1)
Semi-Solid (%)	11 (64.7)	10 (58.8)	11 (68.8)	8 (53.3)	12 (70.6)	17 (54.8)	11 (64.7)	21 (65.6)	6 (54.5)	10 (47.6)
Diarrheal (%)	1 (5.9)	2 (11.8)	0 (0.0)	2 (13.3)	3 (17.6)	5 (16.1)	2 (11.8)	0 (0.0)	1 (9.1)	0 (0.0)

Cross-reference: Section 14.2, Table 11.1.2.7-1
*Median for all values recorded during maintenance phase according to patient diary

TABLE 11.1.2.7B. Stool Consistency During the Maintenance Phase by Absolute Dose of Naloxone - ITT Population with Non-missing Values

Median Stool Consistency During the Maintenance Phase	Absolute Dose of Naloxone			
	Naloxone Placebo	Naloxone 10 mg	Naloxone 20 mg	Naloxone 40 mg
	N=50 (100%)	N=49 (100%)	N=49 (100%)	N=48 (100%)
Entire Maintenance Phase*				
N (%)	50 (100)	48 (100)	49 (100)	47 (100)
Hard (%)	4 (8.0)	5 (10.4)	3 (6.1)	3 (6.4)
Solid (%)	11 (22.0)	15 (31.3)	11 (22.4)	9 (19.1)
Semi-Solid (%)	32 (64.0)	27 (56.3)	32 (65.3)	26 (55.3)
Diarrheal (%)	3 (6.0)	1 (2.1)	3 (6.1)	9 (19.1)

Cross-reference: Section 14.2, Table 11.1.2.7-2
*Median for all values recorded during maintenance phase according to patient diary

TABLE 11.1.2.8A. Laxative Intake at Each Study Visit by Oxycodone/Naloxone Dose Ratio - ITT Population with Non-missing Values

	Dose Ratios									
	40 mg/ Placebo	60 mg/ Placebo	80 mg/ Placebo	1/1	1.5/1	2/1	3/1	4/1	6/1	8/1
Number of days with Laxative Intake	N=17 (100%)	N=17 (100%)	N=16 (100%)	N=15 (100%)	N=17 (100%)	N=32 (100%)	N=17 (100%)	N=32 (100%)	N=11 (100%)	N=22 (100%)
Visit 3 (Randomization)*										
N (n†)	17 (15)	15 (16)	14 (14)	12 (14)	16 (16)	31 (31)	16 (15)	29 (30)	6 (11)	20 (19)
Mean	4.5	4.8	4.6	5.3	5.0	5.2	4.7	4.8	6.3	4.1
SD	3.12	2.54	2.79	2.99	2.88	2.68	2.85	3.10	1.75	3.21
Median	6.0	6.0	6.0	7.0	7.0	7.0	6.0	7.0	7.0	5.5
Min-Max	0-7	0-7	0-7	0-7	0-7	0-7	0-7	0-7	2-7	0-7
Visit 4 (Maintenance)*										
N (n†)	15 (8)	16 (13)	15 (10)	15 (9)	14 (6)	26 (16)	16 (4)	31 (21)	9 (9)	20 (12)
Mean	1.8	2.3	2.3	2.3	1.3	1.9	1.0	2.6	3.2	1.3
SD	2.76	2.46	2.79	2.71	2.05	2.58	2.07	2.74	2.39	1.89
Median	0.0	1.0	1.0	1.0	0.0	0.0	0.0	2.0	4.0	0.5
Min-Max	0-7	0-6	0-7	0-7	0-6	0-7	0-6	0-7	0-6	0-6
Visit 5 (End of Maintenance)*										
N (n†)	14 (10)	15 (13)	14 (12)	12 (8)	13 (5)	26 (13)	10 (4)	26 (17)	7 (8)	19 (10)
Mean	3.9	3.8	4.1	1.8	1.2	1.9	1.0	3.3	3.1	1.7
SD	3.30	3.55	3.52	3.17	2.61	3.15	2.31	3.53	3.63	2.94
Median	5.0	7.0	7.0	0.0	0.0	0.0	0.0	0.5	1.0	0.0
Min-Max	0-7	0-7	0-7	0-7	0-7	0-7	0-7	0-7	0-7	0-7
Visit 6 (End of Follow-up)*										
N (n†)	13 (10)	15 (14)	14 (13)	12 (11)	11 (11)	24 (21)	11 (8)	24 (19)	6 (6)	13 (14)
Mean	3.8	4.0	4.5	2.8	3.4	4.0	2.3	4.1	3.5	3.9
SD	3.63	3.09	3.35	3.38	3.50	3.38	3.10	3.53	3.83	3.50
Median	7.0	5.0	7.0	0.5	1.0	7.0	1.0	7.0	3.5	7.0
Min-Max	0-7	0-7	0-7	0-7	0-7	0-7	0-7	0-7	0-7	0-7
Entire Maintenance Phase**										
N (n†)	15 (12)	16 (15)	16 (14)	15 (10)	15 (9)	26 (24)	16 (9)	32 (25)	9 (9)	21 (17)
Mean	42.9	44.8	51.2	33.4	21.7	31.1	20.4	43.8	44.2	25.1
SD	44.60	43.84	42.37	42.87	39.71	41.47	39.80	42.57	43.13	33.54
Median	25.0	31.3	60.7	15.8	0.0	7.0	0.0	24.6	39.3	7.7
Min-Max	0-100	0-100	0-100	0-100	0-100	0-100	0-100	0-100	0-100	0-100

Cross-reference: Section 14.2, Table 11.1.2.8-1.1

*Number of days with laxation intake during the last 7 days according to patient diary; **Percentage of days with laxation intake during the maintenance phase according to patient diary n† Number of patients taking laxatives

11.1.2.9. Mean laxative Dose

Percentage change in mean laxative dose (ITT population) by oxycodone/naloxone dose ratio, absolute dose of naloxone and by absolute dose of naloxone given the same oxycodone/naloxone dose ratio is summarized in Tables 11.1.2.9-1.1, 11.1.2.9-1.2 and 11.1.2.9-1.3 (Section 14.2). Table 11.1.2.9-2 (Section 14.2) presents the test for difference between each dose of naloxone and placebo. Duration of laxation and mean laxative dose is presented in Listing 11.1.2-3c, Appendix 16.2.

Percentage change in laxative dose by oxycodone/naloxone dose ratio and by absolute dose of naloxone at each study visit is summarized in Table 11.1.2.9A and 11.1.2.9B below.

For each dose ratio, the number of patients qualifying for this analysis was small and varied at each study visit (see also Sections 9.7.1.2.2.9 and 9.8.2). In addition, there was a large variation observed and therefore no clear trends in percentage change in mean laxative dose could be observed for any dose ratio. For each treatment group similar problems were encountered and no firm conclusions can be made regarding the effect of naloxone dose on mean laxative use. The results of this analysis are therefore inconclusive, however, there is no indication from these data that the observed bowel function treatment responses were biased by differences in laxative use.

TABLE 11.1.2.9B. Percentage Change in Laxative Dose at Each Study Visit by Absolute Dose of Naloxone - ITT Population with Non-missing Values

Percentage Change in Mean Laxative Dose	Absolute Dose of Naloxone			
	Naloxone Placebo N=50 (100%)	Naloxone 10 mg N=49 (100%)	Naloxone 20 mg N=49 (100%)	Naloxone 40 mg N=48 (100%)
Visit 4 (Maintenance)*				
N	13	15	14	12
Mean	9.9	-32.6	-21.2	-7.7
SD	103.92	37.95	37.55	73.00
Median	-41.7	-10.1	-3.8	0.0
Min-Max	-71.4-300.0	-91.7-16.7	-83.3-33.3	-83.3-200.0
Visit 5 (End of Maintenance)*				
N	17	11	10	5
Mean	48.7	-9.5	17.9	0.0
SD	99.27	32.01	35.85	0.00
Median	16.7	0.0	16.7	0.0
Min-Max	-93.7-276.2	-89.3-16.7	-57.1-66.8	0.0-0.0
Visit 6 (End of Follow-up)*				
N	17	11	16	10
Mean	67.5	-2.8	16.2	-9.7
SD	164.83	13.66	41.50	49.66
Median	0.0	0.0	7.1	0.0
Min-Max	-56.2-600.0	-26.3-16.7	-80.0-117.8	-81.0-100.0

Cross-reference: Section 14.2, Table 11.1.2.9-1.2
Note: Only patients taking one type of laxative during the entire study are included; *Percentage change from Visit 3 (randomization) in mean laxative dose during the last 7 days according to patient diary

TABLE 11.1.2.10A. Global Assessment by Oxycodone/Naloxone Dose Ratio - ITT Population with Non-missing Values

	Dose Ratios									
Assessment at end of maintenance phase (n, (%))	40 mg/ Placebo N=17 (100%)	60 mg/ Placebo N=17 (100%)	80 mg/ Placebo N=16 (100%)	1/1 N=15 (100%)	1.5/1 N=17 (100%)	2/1 N=32 (100%)	3/1 N=17 (100%)	4/1 N=32 (100%)	6/1 N=11 (100%)	8/1 N=22 (100%)
Efficacy (investigator)										
N	14 (82.4)	17 (100)	15 (93.8)	14 (93.3)	14 (82.4)	27 (84.4)	12 (70.6)	29 (90.6)	10 (90.9)	19 (86.4)
Very good	2 (11.8)	2 (11.8)	2 (12.5)	2 (13.3)	3 (17.6)	4 (12.5)	2 (11.8)	5 (15.6)	0 (0.0)	2 (9.1)
Good	8 (47.1)	5 (29.4)	3 (18.8)	9 (60.0)	6 (35.3)	15 (46.9)	8 (47.1)	13 (40.6)	4 (36.4)	7 (31.8)
Fairly good	1 (5.9)	3 (17.6)	3 (18.8)	2 (13.3)	1 (5.9)	5 (15.6)	0 (0.0)	2 (6.3)	1 (9.1)	3 (13.6)
Moderate	1 (5.9)	2 (11.8)	3 (18.8)	1 (6.7)	2 (11.8)	1 (3.1)	1 (5.9)	3 (9.4)	5 (45.5)	4(18.2)
Slightly poor	1 (5.9)	3 (17.6)	1 (6.3)	0 (0.0)	1 (5.9)	1(3.1)	0 (0.0)	1 (3.1)	0 (0.0)	1 (4.5)
Poor	0 (0.0)	1 (5.9)	2 (12.5)	0 (0.0)	0 (0.0)	1 (3.1)	1(5.9)	5 (15.6)	0 (0.0)	2 (9.1)
Very poor	1 (5.9)	1 (5.9)	1 (6.3)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Efficacy (patient)										
N	14 (82.4)	17 (100)	15 (93.8)	14 (93.3)	14 (82.4)	27 (84.4)	12 (70.6)	29 (90.6)	10 (90.9)	19 (86.4)
Very good	1 (5.9)	1 (5.9)	2 (12.5)	2 (13.3)	4 (23.5)	6 (18.8)	2 (11.8)	3 (9.4)	0 (0.0)	1 (4.5)
Good	7 (41.2)	7 (41.2)	2 (12.5)	8 (53.3)	7 (41.2)	13 (40.6)	9 (52.9)	14 (43.8)	3 (27.3)	7 (31.8)
Fairly good	1 (5.9)	2 (11.8)	3 (18.8)	3 (20.0)	0 (0.0)	3 (9.4)	0 (0.0)	4 (12.5)	2 (18.2)	1 (4.5)
Moderate	3 (17.6)	2 (11.8)	4 (25.0)	1 (6.7)	2 (11.8)	3 (9.4)	1 (5.9)	2 (6.3)	4 (36.4)	5 (22.7)
Slightly poor	0 (0.0)	3 (17.6)	1 (6.3)	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	2 (6.3)	1 (9.1)	3 (13.6)
Poor	1 (5.9)	0 (0.0)	3 (18.8)	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	4 (12.5)	0 (0.0)	2 (9.1)
Very poor	1 (5.9)	2 (11.8)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tolerability (investigator)										
N	14 (82.4)	17 (100)	15 (93.8)	14 (93.3)	14 (82.4)	27 (84.4)	12 (70.6)	29 (90.6)	10 (90.9)	19 (86.4)
Very good	2 (11.8)	5 (29.4)	2 (12.5)	3 (20.0)	4 (23.5)	9 (28.1)	4 (23.5)	5 (15.6)	1 (9.1)	5 (22.7)
Good	10 (58.8)	6 (35.3)	11 (68.8)	10 (66.7)	7 (41.2)	13 (40.6)	7 (41.2)	17 (53.1)	6 (54.5)	12 (54.5)
Fairly good	1 (5.9)	1 (5.9)	2 (12.5)	1 (6.7)	2 (11.8)	5 (15.6)	1 (5.9)	4 (12.5)	3 (27.3)	0 (0.0)
Moderate	1 (5.9)	1 (5.9)	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	1 (4.5)
Slightly poor	0 (0.0)	3 (17.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)
Poor	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.3)	0 (0.0)	0 (0.0)
Very poor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tolerability (patient)										
N	14 (82.4)	17 (100)	15 (93.8)	14 (93.3)	14 (82.4)	27 (84.4)	12 (70.6)	29 (90.6)	10 (90.9)	19 (86.4)
Very good	1 (5.9)	4 (23.5)	2 (12.5)	2 (13.3)	3 (17.6)	7 (21.9)	3 (17.6)	5 (15.6)	1 (9.1)	5 (22.7)
Good	10 (58.8)	7 (41.2)	9 (56.3)	10 (66.7)	8 (47.1)	15 (46.9)	8 (47.1)	17 (53.1)	6 (54.5)	12 (54.5)
Fairly good	1 (5.9)	2 (11.8)	2 (12.5)	2 (13.3)	1 (5.9)	3 (9.4)	1 (5.9)	3 (9.4)	3 (27.3)	0 (0.0)
Moderate	1 (5.9)	1 (5.9)	2 (12.5)	0 (0.0)	2 (11.8)	2 (6.3)	0 (0.0)	2 (6.3)	0 (0.0)	1 (4.5)
Slightly poor	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	1 (4.5)
Poor	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Very poor	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)

Cross-reference: Section 14.2, Table 11.1.2.12-1

TABLE 11.1.2.10B. Global Assessment by Absolute Dose of Naloxone - ITT Population with Non-missing Values

	Absolute Dose of Naloxone			
Assessment at end of maintenance phase (n, (%))	Naloxone Placebo N=50 (100%)	Naloxone 10 mg N=49 (100%)	Naloxone 20 mg N=49 (100%)	Naloxone 40 mg N=48 (100%)
Efficacy (investigator)				
N	46 (92.0)	42 (85.7)	43 (87.8)	40 (83.3)
Very good	6 (12.0)	5 (10.2)	6 (12.2)	7 (14.6)
Good	16 (32.0)	18 (36.7)	23 (46.9)	21 (43.8)
Fairly good	7 (14.0)	6 (12.2)	3 (6.1)	5 (10.4)
Moderate	6 (12.0)	10 (20.4)	4 (8.2)	3 (6.3)
Slightly poor	5 (10.0)	1 (2.0)	1 (2.0)	2 (4.2)
Poor	3 (6.0)	2 (4.1)	6 (12.2)	1 (2.1)
very poor	3 (6.0)	0 (0.0)	0 (0.0)	1 (2.1)
Efficacy (patient)				
N	46 (92.0)	42 (85.7)	43 (87.8)	40 (83.3)
Very good	4 (8.0)	3 (6.1)	5 (10.2)	10 (20.8)
Good	16 (32.0)	18 (36.7)	24 (49.0)	19 (39.6)
Fairly good	6 (12.0)	5 (10.2)	4 (8.2)	4 (8.3)
Moderate	9 (18.0)	10 (20.4)	4 (8.2)	4 (8.3)
Slightly poor	4 (8.0)	4 (8.2)	2 (4.1)	1 (2.1)
Poor	4 (8.0)	2 (4.1)	4 (8.2)	1 (2.1)
very poor	3 (6.0)	0 (0.0)	0 (0.0)	1 (2.1)
Tolerability (investigator)				
N	46 (92.0)	42 (85.7)	43 (87.8)	40 (83.3)
Very good	9 (18.0)	8 (16.3)	13 (26.5)	10 (20.8)
Good	27 (54.0)	27 (55.1)	21 (42.9)	24 (50.0)
Fairly good	4 (8.0)	5 (10.2)	6 (12.2)	5 (10.4)
Moderate	2 (4.0)	1 (2.0)	1 (2.0)	1 (2.1)
Slightly poor	3 (6.0)	1 (2.0)	0 (0.0)	0 (0.0)
Poor	1 (2.0)	0 (0.0)	2 (4.1)	0 (0.0)
very poor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tolerability (patient)				
N	46 (92.0)	42 (85.7)	43 (87.8)	40 (83.3)
Very good	7 (14.0)	9 (18.4)	9 (18.4)	8 (16.7)
Good	26 (52.0)	26 (53.1)	25 (51.0)	25 (52.1)
Fairly good	5 (10.0)	5 (10.2)	3 (6.1)	5 (10.4)
Moderate	4 (8.0)	1 (2.0)	4 (8.2)	2 (4.2)
Slightly poor	2 (4.0)	1 (2.0)	1 (2.0)	0 (0.0)
Poor	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
very poor	1 (2.0)	0 (0.0)	1 (2.0)	0 (0.0)

Cross-reference: Section 14.2, Table 11.1.2.12-2

11.1.2.11. Bowel Index

Tables for the model-estimated responses for daily oxycodone dose versus oxycodone / naloxone ratio, daily naloxone dose versus oxycodone / naloxone ratio, and daily oxycodone dose versus daily naloxone dose are provided in Tables 12.7-1.1 and 12.7-1.2, Section 14.2. The response surface plots are provided in Figures 11.1.6.1.1-1 and 11.1.6.1.1-2, Section 14.2. An ANCOVA analysis with naloxone treatment as a variable factor and baseline bowel index value as covariable was conducted, as well as t-tests comparing naloxone placebo with each naloxone treatment group separately.

The response surface plots for Bowel Index, which also took laxative use into consideration, show that bowel function improved with increasing doses of naloxone at every dose of oxycodone. Similar plots were obtained whether the assigned or randomized dose group was used to generate the data.

11.1.3. Statistical/Analytical Issues

The statistical analysis was carried out as defined in the protocol and in Section 9.7 with the amendments documented in Section 9.8.

11.2. Pharmacology Results

Not investigated.

11.3. Efficacy Discussion and Conclusions

Administration of the oxycodone/naloxone combination was not associated with clinically important differences in the intensity of mean pain or in daily pain intensity, according to dose ratios or absolute dose of naloxone compared to oxycodone/naloxone placebo.

Bowel function stayed almost constant within the ratios of oxycodone/naloxone tested in this study and the level of improvement appeared to increase as the absolute dose of naloxone increased.

A trend towards improved mean bowel function with increased dose of naloxone was seen with the lowest scale values for mean bowel function (representing an improvement in bowel function) at the 1/1, 1.5/1 and 2/1 dose ratios or at an absolute dose of 40 mg naloxone. The oxycodone/naloxone combination provided improvements in ease of defecation, feeling of incomplete bowel evacuation and judgment of constipation. The greatest improvements were seen at dose ratios of 1/1, 1.5/1 and 2/1 or an absolute dose of 40 mg. Modeled estimates of overall treatment effect for specific ratios showed minimal improvement in bowel function between the 2/1 ratio and the 1.5/1 ratio, suggesting that the improvement in bowel function reaches a plateau at the 2/1 ratio.

No identifiable trend was observed in the numbers of patients taking rescue medication when compared across all dose ratios. When comparing the absolute amount of oxycodone taken as rescue medication by naloxone group, a statistically significant difference to placebo was obtained for the 10 mg and 20 mg naloxone groups. However, this difference was not considered to be of any clinical relevance

There was a trend towards an increase in stool frequency with an increase in naloxone dose and a median stool consistency of semi-solid was recorded for the majority of patients. For

identified (Table 12.1A) with a relatively large variation in the incidence of AEs between individual dose ratios (range 47.1% - 88.9%). The incidence of SAEs was low and generally comparable across all naloxone active treatment groups. Eight patients had a total of 10 SAEs during the maintenance phase; 1, 5, 1 and 3 in the placebo, 10 mg, 20 mg and 40 mg naloxone treatment groups respectively (Table 12.1B). No deaths were reported during the study.

The incidence of AEs during the follow-up phase was also comparable between oxycodone dose groups (range 16.7% - 24.6%), with one SAE reported for the 40 mg oxycodone dose group. In addition, during the titration/run-in phase 45.8% of all patients (n=227) had an AE and one SAE occurred (see Tables 12.1-1.4 and 12.1-1.5, Section 14.3). Summaries of AEs during the follow-up phase and titration/run-in phase are provided in Section 14.3.

Table 12.1C summarizes AEs during the maintenance phase by oxycodone/naloxone dose ratio (reported by ≥ 20% of patients in any dose ratio group) and system organ class. The incidence is presented in decreasing order of frequency across all dose ratios. The most frequently reported system organ class affected was gastrointestinal disorders (92 patients, 45.5%) although there was no clear trend in the total incidence for any dose ratio; however, a trend towards increased incidence within this system organ class with increasing naloxone dose was seen. AEs in this system organ class were reported for 19 (38.0%), 22 (43.1%), 24 (47.1%) and 27 (54.0%) patients in the placebo, 10 mg, 20 mg and 40 mg treatment groups (Table 12.1D). In addition, the reported incidence of gastrointestinal disorders was higher among those patients receiving the higher of each dose of naloxone in the same oxycodone/naloxone dose ratio groups (Table 12.2-2.3, Section 14.3). No clear pattern could be identified for the other system organ classes.

Table 12.1E summarizes AEs during the maintenance phase by oxycodone/naloxone dose ratio (reported by ≥ 20% of patients in any dose ratio group) and preferred term in decreasing order of total frequency. Sweating increased (51 patients, 25.2%), diarrhea (46 patients, 22.8%), nausea, abdominal pain, restlessness, muscle cramps, sedation, headache and vertigo were the most frequent AEs. The only major difference between dose ratio treatment groups was the incidence of diarrhea in 50% of patients in the 1.5/1 dose ratio group. The incidence of diarrhea was 50% in the 1.5/1 dose ratio group and 29.4% in the 2/1 dose ratio group. The incidence of diarrhea was higher amongst patients taking active naloxone and increased with higher doses (6 patients (12%), 10 patients (19.6%), 12 patients (23.5%), 18 patients (36.0%) for placebo, 10 mg, 20 mg and 40 mg naloxone respectively (Table 12.1F)). This trend was also observed for the analysis of AEs by absolute dose of naloxone given the same dose ratio of oxycodone/naloxone (Table 12.1-3.3, Section 14.3). Nausea, vomiting and sedation are opioid typical adverse events (see Section 9.7.1.2.2.10). Abdominal pain, cramping and diarrhea are naloxone typical adverse events (see Section 9.7.1.2.2.11).

TABLE 12.1B. Overall Summary of Adverse Events During the Maintenance Phase by Absolute Dose of Naloxone - Safety Population

	Absolute Dose of Naloxone							
	Naloxone Placebo		Naloxone 10 mg		Naloxone 20 mg		Naloxone 40 mg	
	N=50 (100%)		N=51 (100%)		N=51 (100%)		N=50 (100%)	
Category	E	N (%)	E	N (%)	E	N (%)	E	N (%)
Adverse Events	111	32 (64.0)	119	35 (68.6)	129	32 (62.7)	140	35 (70.0)
Causally Related#	74	25 (50.0)	93	26 (51.0)	100	27 (52.9)	109	30 (60.0)
Leading to discontinuation of study drug	1	1 (2.0)	13	5 (9.8)	29	6 (11.8)	30	9 (18.0)
Serious Adverse Events	1	1 (2.0)	5	3 (5.9)	1	1 (2.0)	3	3 (6.0)
Causally Related#	0	0 (0.0)	3	1 (2.0)	0	0 (0.0)	2	2 (4.0)
Leading to discontinuation of study drug	1	1 (2.0)	5	3 (5.9)	1	1 (2.0)	3	3 (6.0)
Deaths	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)

Cross-reference: Section 14.3, Table 12.1-1.2
E = Number of events
# = Related adverse events include all events listed with a definite, probable, possible or unknown/missing relationship to study drug

TABLE 12.1D. Adverse Events During the Maintenance Phase by Absolute Dose of Naloxone (Reported by ≥ 10% of Patients) and System Organ Class - Safety Population

System Organ Class	Absolute Dose of Naloxone							
	Naloxone Placebo		Naloxone 10 mg		Naloxone 20 mg		Naloxone 40 mg	
	N=50 (100%)		N=51 (100%)		N=51 (100%)		N=50 (100%)	
	N	(%)	N	(%)	N	(%)	N	(%)
Gastrointestinal Disorders	19	(38.0)	22	(43.1)	24	(47.1)	27	(54.0)
Skin and Subcutaneous Tissue Disorders	16	(32.0)	17	(33.3)	16	(31.4)	16	(32.0)
Nervous System Disorders	17	(34.0)	9	(17.6)	11	(21.6)	14	(28.0)
Musculoskeletal and Connective Tissue Disorders	7	(14.0)	8	(15.7)	13	(25.5)	12	(24.0)
Psychiatric Disorders	11	(22.0)	10	(19.6)	8	(15.7)	11	(22.0)
Ear and Labyrinth Disorders	8	(16.0)	6	(11.8)	4	(7.8)	6	(12.0)
General disorders and administration site conditions	0	(0.0)	5	(9.8)	4	(7.8)	5	(10.0)

Cross-reference: Section 14.3, Table 12.1-2.2

TABLE 12.1F. Adverse Events During the Maintenance Phase by Absolute Dose of Naloxone (Reported by ≥ 10% of Patients) and Preferred Term - Safety Population

Preferred Term	Absolute Dose of Naloxone							
	Naloxone Placebo		Naloxone 10 mg		Naloxone 20 mg		Naloxone 40 mg	
	N=50 (100%)		N=51 (100%)		N=51 (100%)		N=50 (100%)	
	N	(%)	N	(%)	N	(%)	N	(%)
Sweating Increased	15	(30.0)	14	(27.5)	9	(17.6)	13	(26.0)
Diarrhoea NOS	6	(12)	10	(19.6)	12	(23.5)	18	(36.0)
Abdominal Pain NOS	8	(16.0)	5	(9.8)	15	(29.4)	11	(22.0)
Nausea	8	(16.0)	11	(21.6)	10	(19.6)	11	(22.0)
Restlessness	11	(22.0)	10	(19.6)	8	(15.7)	10	(20.0)
Muscle Cramps	5	(10.0)	6	(11.8)	9	(17.6)	10	(20.0)
Sedation	11	(22.0)	6	(11.8)	4	(7.8)	8	(16.0)
Headache NOS	7	(14.0)	6	(11.8)	5	(9.8)	8	(16.0)
Vertigo	8	(16.0)	6	(11.8)	4	(7.8)	6	(12.0)
Skin Disorder NOS	3	(6.0)	4	(7.8)	5	(9.8)	7	(14.0)
Vomiting NOS	5	(10.0)	2	(3.9)	5	(9.8)	4	(8.0)

Cross-reference: Section 14.3, Table 12.1-3.2

During follow-up a small proportion of patients had a causally related AE in each oxycodone dose group (range 10.6% - 13.8 %). During the titration/run-in phase 36.6% of all patients (n=227) had a causally related AE (See Tables 12.1-1.4 and 12.1-1.5, Section 14.3).

12.1.3. Action Taken

AEs including the action taken are presented in Listing 12.1-1, Appendix 16.2.

No separate analyses of action taken was performed.

12.2. Deaths, Other Serious Adverse Events, and Other Significant Events

AEs leading to death during the maintenance phase are summarized by oxycodone/naloxone dose ratio, absolute dose of naloxone and by absolute dose of naloxone given the same oxycodone/naloxone dose ratio in Tables 12.2-1.1, 12.2-1.2 and 12.2-1.3, Section 14.3. Adverse events leading to death during the follow-up phase by absolute dose of oxycodone (safety population) are presented in Table 12.2-1.4, Section 14.3 and adverse events leading to death in the titration phase (titration phase population) are presented in Table 12.2-1.5, Section 14.3. Details of deaths during the study are provided in Listing 12.2-1, Appendix 16.2.

SAEs (system organ class and preferred term) for oxycodone/naloxone dose ratio, absolute dose of naloxone and absolute dose of naloxone given the same oxycodone/naloxone dose ratio are presented for the maintenance phase (safety population) in Tables 12.2-2.1, 12.2-2.2 and 12.2-2.3, Section 14.3, for the follow-up phase (safety population) by absolute dose of oxycodone in Table 12.2-2.4, Section 14.3 and for the titration phase (titration phase population) in Table 12.2-2.5, Section 14.3.

Listing 12.2-2, Appendix 16.2 presents details of all SAEs.

12.2.1. Deaths

No deaths were reported during the study.

12.2.2. Other Serious Adverse Events

A total of eight patients had 10 SAEs during the maintenance phase and the incidence was generally comparable across all treatment groups (1 patient (2.0%), 3 patients (5.9%), 1 patient (2.0%) and 3 patients (6.0%) in the placebo, 10 mg, 20 mg and 40 mg naloxone treatment groups (Table 12.2-2.2, Section 14.3). One additional patient (06 V141) experienced a SAE during the titration phase; and one patient (14 068) experienced a SAE during the follow-up phase. Both of these SAEs were assessed as not related to study medication and narratives are provided in Section 14.3.1.

Table 12.2.2 summarizes the ten SAEs during the maintenance phase by patient. Ten SAEs were reported in eight patients, three were gastrointestinal disorders (2 diarrhea, 1 nausea). A narrative for each patient who had a SAE is contained in Section 14.3.1.

All eight patients with SAEs during the maintenance phase discontinued the study (Table 12.1-1.2, Section 14.3).

unable to work for some time

▲ upon internal review of source documentation additional terms have been coded:

patient	AE
01 162	Fever, Abdominal Pain, Headache
33 215	Fall
33 203	Hypertension aggravated, Vomiting, Tremor
25 214	Hemiparesis, Speech Disorder, Syncope, Diarrhea, Vomiting
01 094	Withdrawal Syndrome, Dyskinesia, Pain, Restlessness, Anxiety, Respiratory distress
27 001	Abdominal Pain

TABLE 12.2.3.1A. Adverse Events Leading to Discontinuation of Study Medication During the Maintenance Phase by Oxycodone/Naloxone Dose Ratio and Preferred Term - Safety Population

	Dose Ratios									
Preferred Term	40 mg/ Placebo N=17 (100%)	60 mg/ Placebo N=17 (100%)	80 mg/ Placebo N=16 (100%)	1/1 N=15 (100%)	1.5/1 N=18 (100%)	2/1 N=34 (100%)	3/1 N=18 (100%)	4/1 N=33 (100%)	6/1 N=12 (100%)	8/1 N=22 (100%)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Diarrhea NOS	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	3 (16.7)	3 (8.8)	3 (16.7)	0 (0.0)	0 (0.0)	1 (4.5)
Muscle cramps	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	1 (5.6)	3 (8.8)	1 (5.6)	0 (0.0)	0 (0.0)	1 (4.5)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	1 (5.6)	1 (2.9)	1 (5.6)	1 (3.0)	0 (0.0)	1 (4.5)
Restlessness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.9)	2 (11.1)	0 (0.0)	0 (0.0)	1 (4.5)
Sweating increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (2.9)	1 (5.6)	0 (0.0)	0 (0.0)	1 (4.5)
Tremor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	3 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal Pain NOS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	2 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
Anxiety	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Feeling hot and cold	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting NOS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Vertigo	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Arrhythmia NOS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Tachycardia NOS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lacrimation increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Mydriasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1(5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting aggravated	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Drug withdrawal syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)
Feeling cold	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain exacerbated	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)	0 (0.0)	0 (0.0)
Rigors	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholelithiasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)
Sarcoidosis NOS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Femur fracture	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Muscle twitching	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Myalgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache NOS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)
Sedation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Transient ischaemic attack	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psychotic disorder NOS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Chronic obstructive airways disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)
Rhinorrhoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Yawning	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Piloerection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension aggravated	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Cross-reference: Section 14.3, Table 12.2-3.1

Safety Assessment Summary for Subjects Who Discontinued OXN2401 Due to Diarrhea or Opioid Withdrawal Symptoms

There were altogether 13 subjects (safety population n= 202) who discontinued the OXN2401 clinical trial due to diarrhea (subjects with AE diarrhea with the action taken regarding study medication noted as "discontinued") or opioid withdrawal symptoms (subjects with signs of withdrawal as an AE or signs of withdrawal) as the main documented reason. Upon further review, the AEs, SOWS and rescue medication of these patients have been analyzed in order to evaluate whether withdrawal might have also been an issue in theses patients who discontinued the trial primarily due to diarrhea (or vice versa).

The case review and assessment for each individual case is separately attached in the narratives (see Section 14.3.1).

Most of these patients did not have a good pain control on oxycodone alone.

Overall there were three patients who discontinued due to documented signs of withdrawal. One of these three discontinued due to documented diarrhea as well, and experienced signs or symptoms which are consistent with withdrawal symptoms prior to randomization.

Ten patients discontinued due to diarrhea (AE "diarrhea" with action taken regarding study medication "discontinued").

Two of these ten patients who discontinued due to diarrhea demonstrated a plausible adverse event profile and SOWS data to support this reason for discontinuation. These two patients experienced signs or symptoms which are consistent with withdrawal symptoms prior to randomization. After randomization, non-gastrointestinal AEs which could be consistent with possible withdrawal were not documented.

Eight of these ten patients discontinued due to diarrhea and also had a high SOWS score or additional signs or symptoms of withdrawal in the AE report, leading to the suspicion that withdrawal might also have been a reason for the discontinuation. However, it is noteworthy that five of these eight patients experienced signs or symptoms which are consistent with withdrawal prior to randomization.

The other three of the eight patients did neither experience signs or symptoms which are consistent with withdrawal prior to randomization nor non-gastrointestinal AEs which could be consistent with possible withdrawal post randomization.

These observations do not appear to be influenced by consumption of rescue medication.

In conclusion, the true number of patients who discontinued the study due to signs or symptoms of withdrawal might be slightly higher than indicated by the investigator's assessment.

These data suggest that analysis of the dose-response data for patients transferring to OXN may be complicated for those whose pain was not well controlled by oxycodone alone, and particularly for those who have established physical dependence on higher doses of opioids.

Taken together, no clear assessment of the investigated dose ratios is possible with regard to the risk for patients of developing diarrhea or withdrawal syndromes. A trend might exist in that higher incidences for diarrhea and withdrawal symptoms occur with increasing doses of oxycodone (from 40 mg to 60 mg, with a tapering off at 80 mg) as well as with increasing doses of naloxone without revealing a clear advantage for one of the chosen dose ratios.

12.4. Vital Signs

Vital sign measurements (e.g. systolic blood pressure, diastolic blood pressure, heart rate, respiration, temperature) were not performed during the study.

12.5. Other Observations Related to Safety

Listings of pregnancy/lactation and investigator comments are provided in Listing 12.2-4 and 12.4-1, Appendix 16.2, respectively.

12.5.1. Sumscore of the Severity of Elicited Opioid Typical Adverse events

Tables 11.1.2.10-1.1, 11.1.2.10-1.2 and 11.1.2.10-1.3, Section 14.2, summarize the sumscore of severity of elicited opioid typical adverse events for the ITT population by oxycodone/naloxone dose ratio, absolute dose of naloxone and by absolute dose of naloxone given the same oxycodone/naloxone dose ratio. The test for difference for each naloxone dose versus placebo is given in Table 11.1.2.10-2, Section 14.2. The sumscore of the severity of elicited opioid typical adverse events during the follow-up phase by absolute dose of oxycodone is summarized in Table 11.1.2.10-3, Section 14.2. Listing 11.1.2-5, Appendix 16.2, presents the sumscore of severity of elicited opioid and naloxone typical adverse events for each patient over the duration of the study. Elicited AEs are presented in Listings 12.1-1 and 12.1-2, Appendix 16.2.

Sumscores for elicited opioid typical adverse events at each study visit by oxycodone/naloxone dose ratio and by absolute dose of naloxone are summarized in Table 11.1.2.10A and 11.1.2.10B below.

For all treatment groups and dose ratios mean sumscores were generally low at each study visit and during the entire maintenance phase. The highest mean sumscores (split by treatment group and dose ratio) for the entire maintenance phase occurred in the 40 mg naloxone group (1.4±2.27) and the 1.5/1 dose ratio group (2.2±2.91). During the maintenance phase there was a clear trend for a reduction in mean sumscores for all naloxone treatment groups and naloxone dose ratios when compared to placebo (Tables 11.1.2.10A and 11.1.2.10B). At the end of the maintenance phase, the mean sumscores were lower in the naloxone treatment groups than in the placebo group (Table 11.1.2.10B) with a statistically significant difference ($p<0.05$) for all naloxone treatment groups (Table 11.1.2.10-2, Section 14.2).

Analysis by absolute dose of naloxone given the same oxycodone/naloxone dose ratio shows no identifiable differences between the absolute dose of naloxone within either dose ratio group (4/1 and 2/1) (Table 11.1.2.10-1.3).

TABLE 12.5.1B. Sumscores for Elicited Opioid Typical Adverse events at Each Study Visit by Absolute Dose of Naloxone - ITT Population with Non-missing Values

	Absolute Dose of Naloxone			
Sumscores	Naloxone Placebo N=50 (100%)	Naloxone 10 mg N=49 (100%)	Naloxone 20 mg N=49 (100%)	Naloxone 40 mg N=48 (100%)
Visit 3 (Randomization)*				
N (n†)	50 (10)	49 (15)	49 (16)	48 (10)
Mean	0.6	0.9	0.9	0.3
SD	1.39	1.67	1.53	0.75
Median	0.0	0.0	0.0	0.0
Min-Max	0-5	0-7	0-5	0-3
Visit 4 (Maintenance)*				
N (n†)	48 (18)	47 (16)	47 (17)	43 (14)
Mean	0.7	0.7	0.8	0.9
SD	1.23	1.26	1.63	1.94
Median	0.0	0.0	0.0	0.0
Min-Max	0-5	0-5	0-8	0-10
Visit 5 (End of Maintenance)*				
N (n†)	46 (11)	42 (7)	43 (3)	41 (2)
Mean	0.7	0.3	0.1	0.1
SD	1.34	0.63	0.50	0.49
Median	0.0	0.0	0.0	0.0
Min-Max	0-5	0-2	0-3	0-3
Visit 6 (End of Follow-up)*				
N (n†)	45 (6)	41 (2)	41 (2)	39 (5)
Mean	0.2	0.0	0.1	0.2
SD	0.70	0.22	0.49	0.51
Median	0.0	0.0	0.0	0.0
Min-Max	0-4	0-1	0-3	0-2
Entire Maintenance Phase**				
N (n†)	48 (25)	47 (23)	47 (23)	44 (20)
Mean	1.3	1.2	1.2	1.4
SD	1.67	1.61	1.88	2.27
Median	1.0	0.0	0.0	0.0
Min-Max	0-6	0-6	0-8	0-10

Cross-reference: Section 14.2, Table 11.1.2.10-1.2
*Sumscores for elicited adverse events during the last 7 days; **Sumscores for elicited adverse events during the entire maintenance phase
n† Number of patients with at least one elicited opioid typical side effect

TABLE 12.5.2A. Sumscores for Elicited Naloxone Typical Adverse events at Each Study Visit by Oxycodone/Naloxone Dose Ratio - ITT Population with Non-missing Values

	Dose Ratios									
Sumscores	40 mg/ Placebo N=17 (100%)	60 mg/ Placebo N=17 (100%)	80 mg/ Placebo N=16 (100%)	1/1 N=15 (100%)	1.5/1 N=17 (100%)	2/1 N=32 (100%)	3/1 N=17 (100%)	4/1 N=32 (100%)	6/1 N=11 (100%)	8/1 N=22 (100%)
Visit 4 (Maintenance)*										
N (n†)	15 (1)	17 (5)	16 (0)	15 (3)	15 (6)	28 (6)	16 (5)	31 (8)	11 (2)	21 (2)
Mean	0.1	0.4	0.0	0.7	1.1	0.7	0.8	0.6	0.4	0.4
SD	0.26	0.71	0.0	1.71	2.12	1.44	1.47	1.38	0.81	1.43
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Min-Max	0-1	0-2	0-0	0-6	0-8	0-4	0-4	0-6	0-2	0-6
Visit 5 (End of Maintenance)*										
N (n†)	14 (1)	17 (4)	15 (1)	14 (0)	14 (4)	28 (4)	12 (0)	29 (3)	10 (1)	19 (1)
Mean	0.1	0.3	0.1	0.0	0.4	0.4	0.0	0.1	0.2	0.1
SD	0.27	0.59	0.26	0.0	0.85	0.99	0.0	0.31	0.63	0.23
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Min-Max	0-1	0-2	0-1	0-0	0-3	0-4	0-0	0-1	0-2	0-1
Entire Maintenance Phase**										
N (n†)	15 (3)	17 (9)	16 (3)	15 (5)	15 (9)	29 (10)	16 (6)	31 (12)	11 (4)	21 (9)
Mean	0.4	0.9	0.3	1.1	1.5	1.2	1.1	1.3	0.8	1.0
SD	1.06	1.11	0.58	1.96	2.20	1.93	1.81	1.88	1.33	1.66
Median	0.0	1.0	0.0	0.0	1.0	0.0	0.0	0.0	0.0	0.0
Min-Max	0-4	0-4	0-2	0-6	0-8	0-6	0-6	0-6	0-4	0-7

Cross-reference: Section 14.2, Table 11.1.2.11-1.1

*Sumscores for elicited adverse events during the last 7 days; **Sumscores for elicited adverse events during the entire maintenance phase

n† Number of patients with at least one elicited naloxone typical side effect

12.5.3. Objective (OOWS) and Subject (SOWS) Opioid Withdrawal Scales

Full listings for OOWS and SOWS data are provided in Listings 10.1-3 and 10.1-4, respectively, in Appendix 16.2.

The results of a post-hoc analysis of SOWS data are provided in Tables 12.4-1.1 to 12.4-4.6 in Section 14.2. Surface plots for minimum, mean, and maximum SOWS data are provided in Figures 11.1.3.1.1-1 to 11.1.4.1.1-1, Section 14.2.

The maximum, minimum, and mean total SOWS were computed for each subject across the 7 days. The relationship of total SOWS score to naloxone and oxycodone dose was examined by fitting these data to a full quadratic model using these factors and their interaction. The analysis produced similar results when either the minimum, mean or maximum total SOWS score for each subject was used to create the model.

A general trend can be observed that with higher doses of naloxone administered there is a slight increase in the predicted values of maximum total SOWS at a low dose of oxycodone and a moderate increase at higher doses of oxycodone (see Table 12.4-3.17). In addition, increasing doses of oxycodone in the combined treatment with naloxone also seem to be associated with an increase in the predicted values which is not necessarily linear and appears to have reached its maximum at 60mg/day (see Tables 12.4-3.13).

OOWS data were available for 4 patients only. Therefore, no analysis of OOWS was performed.

12.6. Safety Discussion and Conclusions

During the double-blind maintenance phase the overall incidence of AEs was comparable across all naloxone groups (placebo, 10 mg, 20 mg and 40 mg). Most AEs were mild or moderate in intensity and did not lead to study drug discontinuation (the discontinuations that did occur are discussed in greater detail below).

The most common reported AEs were those known to be associated with either naloxone or oxycodone and diarrhea was the most frequently reported AE with an incidence of 50% in the 1.5/1 dose ratio group; the incidence was substantially reduced from the 1.5/1 to 2/1 dose ratio group. The incidence of diarrhea increased with higher doses of naloxone. Moreover, diarrhea was the most common causally related AE and AE leading to study drug discontinuation in the 20 mg and 40 mg naloxone treatment groups. No deaths occurred during the study and there were 10 SAEs reported in eight patients during the maintenance phase. For two patients the reported SAEs were gastrointestinal disorders (diarrhea, nausea) that had a probable relationship to study drug.

Discontinuation due to Adverse Events

Of the 36 subjects who discontinued from the study during the maintenance phase, 22 subjects discontinued due to adverse events including signs of withdrawal. All eight subjects with SAEs discontinued from the study. Subjects who discontinued due to diarrhea and/or withdrawal are discussed in greater detail below.

There were altogether 13 subjects (safety population n= 202) who discontinued due to diarrhea (subjects with Adverse Event diarrhea with action taken regarding study medication "discontinued") or opioid withdrawal symptoms (subjects with signs of withdrawal as AE or signs of withdrawal) as the main documented reason. A further review of adverse events, withdrawal symptoms using the SOWS, and rescue medication in these subjects has been performed in

Incidence of Diarrhea by Oxycodone and Naloxone Dose

Total Daily Oxycodone Dose (mg) / Total Daily Naloxone Dose (mg)	40	60	80
0	1/17 (5.9%) ∞	3/17 (17.6%) ∞	2/16 (12.5 %) ∞
10	3/17 (17.6%) 4:1	3/12 (25.0%) 6:1	4/22 (18.2%) 8:1
20	5/17 (29.4%) 2:1	3/18 (16.7%) 3:1	4/16 (25.0%) 4:1
40	4/15 (26.7%) 1:1	9/18 (50.0%) 1.5:1	5/17 (29.4%) 2:1

Entries in each cell are:
- Number of subject's incidence of diarrhea/number of subjects in that dose group
- % of subjects in that dose group
- oxycodone/naloxone dose ratio

Duration of Diarrhea

In general, a trend was observed that with increasing doses of naloxone administered there is an increase in the absolute duration of diarrhea in subjects who completed the clinical trial. Dosage regimens that included the 10 mg naloxone strength seem to possess a lower percentage of days with diarrhea during the total duration of treatment as compared with higher doses of naloxone or naloxone placebo.

Nevertheless, based on the small number of subjects for a safety assessment, no solid and differentiating statement can be made with regard to the different doses and combinations under investigation. On the other hand, no comparatively unfavorable safety data can be detected for the 2:1 ratio of oxycodone and naloxone whereas the 1.5:1 ratio seems to result in a higher incidence and longer duration of diarrhea.

Subjective Opioid Withdrawal Scale (SOWS)

The model-based predicted mean of the maximum total SOWS score for each subject in the first week post-randomization is summarized in the table below.

Subjects were asked to report the occurrence of subjective opioid withdrawal in their diaries during the first week of treatment with naloxone. These were captured using the SOWS, which rated 16 symptoms on a scale of 0 (not at all), to 4 (extremely). A total SOWS score (ranging from 0 to 64) was computed by summing the scores across the 16 symptoms. The maximum, minimum, and mean total SOWS were computed for each subject across the 7 days. The relationship of total SOWS score to naloxone and oxycodone dose was examined by fitting these data to a full quadratic model using these factors and their interaction. The analysis produced similar results when either the minimum, mean or maximum total SOWS score for each subject was used to create the model.

that the enteral administration of naloxone can reverse opioid-induced constipation, potentially by acting as an antagonist of opioid action at the intestinal receptor level [16,17,29-32]. Another identified effect of opioid administration is the development of tolerance. Initial effects of opioid administration in most individuals are analgesia, sedation, nausea/vomiting, respiratory depression, pupillary constriction, constipation and euphoria or dysphoria. However, numerous studies and clinical experience suggest that tolerance to different opioid effects develop at different rates. While tolerance to nausea, vomiting, sedation, euphoria and respiratory depression occur rapidly, there is minimal development of tolerance to constipation and miosis. Tolerance to opioid analgesia does occur, but it does not appear to be a limiting factor and dose escalation in chronic pain therapy normally occurs as a consequence of increasing pain. These differences in tolerability suggest receptor-related differences in the speed and development of tolerance and are a major factor in the abuse potential for a particular opioid. Therefore, it is recognized that a combination product of an opioid with a narcotic antagonist can have therapeutic benefits for chronic pain patients in reducing constipation and the likelihood for abuse. This therapeutic concept has been successfully applied in a combination product (Valoron N®) of the opioid tilidine and the opioid antagonist naloxone. The major theoretical difficulties with a combination such as this are 1) a potential diminution of the analgesic effect and 2) the induction of abstinence (withdrawal) syndrome.

The primary objective of the current study was to investigate whether an oral, CR oxycodone/naloxone combination tablet, intended to be dosed every 12 hours on an ongoing basis, led to a comparable analgesia with a decrease in constipation in patients with severe chronic pain of tumor- and non-tumor origin when compared with CR oxycodone alone. Secondary objectives were to compare the incidence of other adverse events between each treatment group, to assess the effects of opioid-induced tolerance and to provide evidence to support a clinical development program for a potential combination produce of naloxone and oxycodone. The optimal ratio of CR oxycodone to CR naloxone was examined.

Patients received treatment with oxycodone and naloxone CR tablets, with CR oxycodone as rescue medication and patient administered laxatives as necessary.

The present study included 202 randomized patients. The primary efficacy outcomes were pain and bowel function and subjective rating scales were used to assess treatment outcomes. Bowel function was assessed using a combined score of three non-validated rating scales that describe overall constipation: ease of defecation, feeling of incomplete bowel evacuation and personnel judgment of constipation.

Overall, the treatment groups were generally balanced regarding demographic and baseline characteristics, anamnesis and medical profile. A total of 36 (17.8%) patients discontinued during the treatment or follow-up phase with the primary reason for discontinuation being an AE (19 patients, 9.4%).

During the maintenance phase no apparent differences in the intensity of pain were observed between any treatment groups, indicating that there was no clinically meaningful influence of naloxone on the analgesic effect of oxycodone. This effect was consistent for each treatment group and for each naloxone/oxycodone dose ratio. Analyzed by absolute naloxone dose (10 mg, 20 mg or 40 mg), mean pain scores were equivalent to naloxone placebo ($p<0.05$, one sided t-test for non-inferiority with equivalence limit 8 (ITT population) during the last 7 days prior to Visit 4 and at the end of maintenance.

In contrast, changes in bowel function were observed with different doses of naloxone. There was a trend for an improved mean bowel function with increasing dose of naloxone. During the last 7 days at the end of the maintenance phase, mean bowel function scores were lowest (low score values represent low bowel dysfunction) with the 1/1, 1.5/1 and 2/1 dose ratios (ITT

For laboratory investigations, no trends or possibly treatment related pathologic findings could be identified for any dose of naloxone.

Previous clinical trials have demonstrated the potential for naloxone to reverse or reduce opioid-induced constipation [16,17,29-32]. However, these clinical trials were performed in small patient populations, with widely different therapeutic protocols and the results remain somewhat controversial regarding safety, dosing, and the potential for loss of analgesia. In one such study Meissner et al [16] recommended that the most effective intestinal effect could be achieved by a continuous release of small amounts of naloxone over an extended period. This recommendation is valid given problems with increases in opioid use, reversals in analgesia, excessive gastrointestinal adverse events, and the appearance of systemic withdrawal symptoms when using large single or multiple doses of naloxone [16,17,29,31]. Some placebo effects were also noted [29], but it was thought generally unlikely that placebo would influence laxation. The current trial has been performed in a relatively large patient population and for the first time utilized a CR formulation of both naloxone and oxycodone.

The administration of CR oxycodone and naloxone in combination was not associated with clinically important differences in the intensity of mean pain according to dose ratios or absolute dose of naloxone compared to oxycodone/naloxone placebo. Mean bowel function improved with increasing dose of naloxone as measured by the Numerical Analogue Scale (NAS). Statistically significant improvement in bowel function relative to placebo were found for the 20mg and 40 mg doses of naloxone. The analyses estimates indicate that the bowel function improvement increases as the oxycodone/naloxone ratio decreases, with the estimated improvement at 2:1 ratio approximately 50 % higher than at 4:1 ratio and with a minimal improvement from the 2:1 ratio to the 1.5:1 ratio. Improvement in bowel function associated with CR oxycodone and CR naloxone was observed for each of the 3 components of the NAS scale (ease of defecation, feeling of incomplete bowel evacuation and judgment of constipation). CR oxycodone and CR naloxone appeared to be well tolerated. The most common treatment related adverse event was diarrhea, which appeared to be dose related. Based on a review of the efficacy and safety results by dose and dose ratio, the 2/1 ratio with a 40 mg maximum daily dose of naloxone appears to be best suited for further evaluation.